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ORGANIC SEMINAR

ABSTRACTS

Summer 1947

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ORGANIC SEMINAR ABSTRACTS

Summer, 1947

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BASIC PRINCIPLES OF ELECTRONIC THEORY

In general a covalent bond between atoms X and Y may break in one of two ways giving rise to two separate and distinct mechanisms by which organic molecules can react.

$X{:}Y \rightarrow X\cdot + \cdot Y$ (Homolytic cleavage - free radicals)

$X{:}Y \rightarrow [X]^{+} + [{:}Y]^{-}$ (Heterolytic cleavage - ions)

In one case the fragments are electrically charged and subject to the usual laws of electrostatic attraction and repulsion. In the other, a highly reactive free electron is present but the fragments have no formal charge. Clearly therefore such reactions will not be subject to the same laws and in discussing mechanisms it is of utmost importance to know which method of bond opening occurs. Frequently this is quite difficult, but often an indication of the nature of the reaction may be obtained by an examination of the characteristics and experimental conditions favorable for reaction.

Characteristics of Free Radical and Ionic Reactions

Free Radical Reactions	Ionic Reactions
1) Catalyzed by light, high temperatures of peroxides.	1) Frequently catalyzed by acids or bases.
2) Proceed in vapor phase or in non-polar solvents.	2) Almost never occur in vapor phase. Facilitated by polar solvents.
3) Aromatic substitution proceeds abnormally insofar as orientation is concerned.	3) Aromatic substitution follows orientation rules.
4) More or less temperature independent.	4) Rate of reaction increases with temperature.
5) Frequently initiated by decomposition reactions. Displacement reactions predominate.	5) Proceed by addition or displacement mechanisms.

Obviously there may be instances in which the mode of fission or reaction changes with the environment of experimental conditions. This can be illustrated with the dissociation of hexaphenyl ethane and the bromination of bromobenzene.

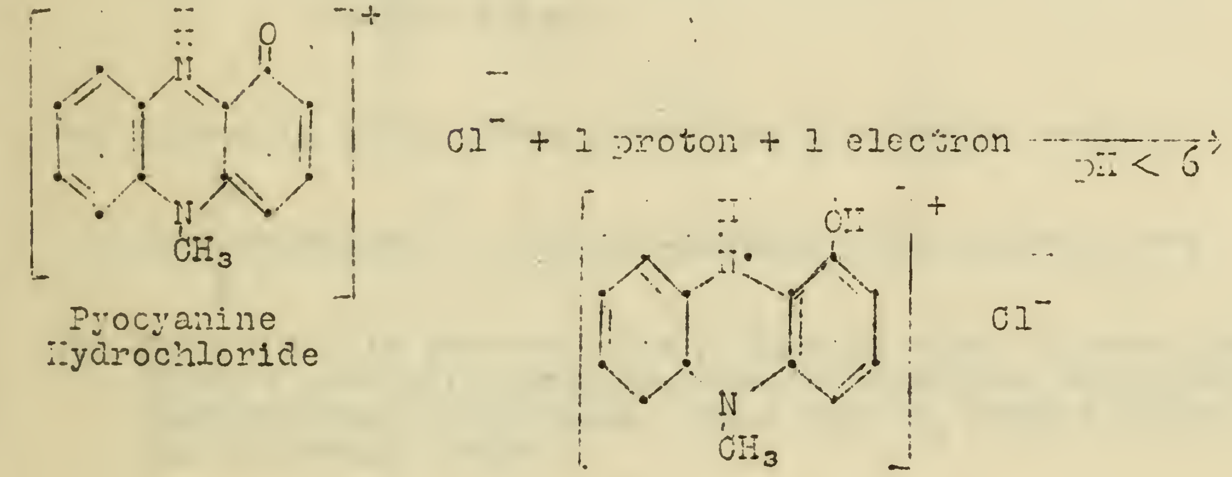
$$\phi_3C\text{-}C\phi_3 \xrightleftharpoons{\text{benzene}} 2\,\phi_3C\cdot$$

$$\phi_3C-C\phi_3 \xrightleftharpoons{SO_2} 2\,[\phi_3C]^+ + [SO_2]^-$$

$$\phi Br \xrightarrow[{[55^\circ]}]{FeBr_3 + Br_2} \begin{array}{l} C_6H_5Br_2 \\ o = 13.4\% \\ m = 1.9\% \\ p = 84.6\% \end{array}$$

$$\xrightarrow[{[500^\circ]}]{FeBr_3 + Br_2} \begin{array}{l} o = 20.9\% \\ m = 55.7\% \\ p = 23.4\% \end{array}$$

The question of reaction mechanisms is complicated still more for there are stable free radicals known which are themselves charged. Pyocyanine and other semiquinones exhibit this phenomenon.



Pyocyanine Hydrochloride

Semiquinone of Pyocyanine

In the subsequent discussion we will be concerned only with the intramolecular transmission of electrical charge and the factors to be considered in dealing with ionic mechanisms.

At least five electrical effects can operate within organic molecules.

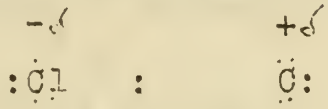
1) Inductive Effect (I_s)
2) Field Effect (D)
3) Inductomeric Effect (I_D)
4) Electromeric Effect (E)
5) Mesomeric Effect (M)

It is possible for some of these effects to operate in opposition and in order to discuss the development of electrical charges within a molecule it is necessary to know both the direction and relative importance of the effects.

1) Characteristics of the Inductive Effect (I_s)

a) It arises because of the fact that in an unsymmetrical covalent bond one atom is inherently more electronegative than the other.

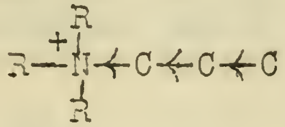
Symmetrical Covalent Bond



Partial Ionic Character of a Covalent Bond

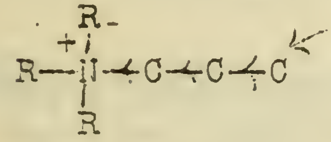
Chlorine is said to exhibit a $-I_s$ effect because the shared electron pair in the C-Cl bond is closer to Cl than in the C-H bond.

b) Changes in electrical character are all in the same direction and represent a permanent condition of the molecule.



$$R-\overset{+}{N}(R)_2 \leftarrow C \leftarrow C \leftarrow C$$

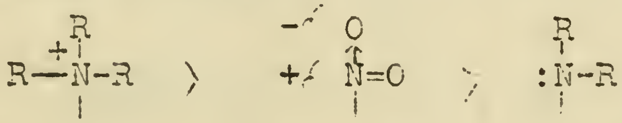
c) Effect is small after more than one carbon atom.



$$R-\overset{+}{N}(R)_2 \leftarrow C \leftarrow C \leftarrow C$$

$-I_s$ of nitrogen atom is weak here

d) The effect is greatest for a charged atom, intermediate for dipoles resulting from coordinate covalence, and smallest for unsymmetrical covalences. Thus the $-I_s$ effect decreases in the following order:

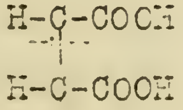


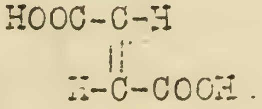
$$R-\overset{+}{N}(R)-R \;>\; \overset{-\delta}{O} \leftarrow \overset{+\delta}{N}=O \;>\; :N(R)-R$$

If the charge on an atom is constant the $-I_s$ effect increases as you go across a row in the periodic table. It decreases as you go down in a given group.

2) Characteristics of the Field Effect (D)

a) It operates thru space rather than over a carbon skeleton. Except in cases of unusual geometry it cannot be differentiated from I_s. The difference in second ionization constants of maleic and fumaric acids seems to indicate that such an effect exists.





$K_1 = 15 \times 10^{-3}$

$K_2 = 2.6 \times 10^{-7}$

$K_1 = 1 \times 10^{-3}$

$K_2 = 300 \times 10^{-7}$

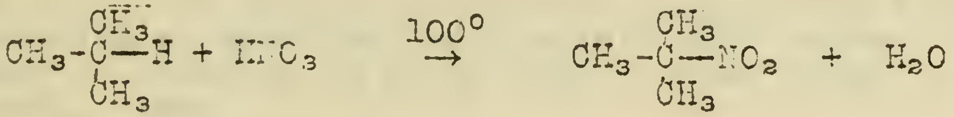
3) Characteristics of the Inductomeric Effect (I_D)

a) It is an electronic displacement which adds to or subtracts from I_s. It is caused by a change in the electrostatic environment produced by the field of the attacking reagent. It corresponds to the polarizability of refraction and dielectric phenomena.

b) It decreases when a unit or fractional charge is placed on an adjacent atom.

c) It decreases as you go across a row in the periodic table. It increases as you go down a group.

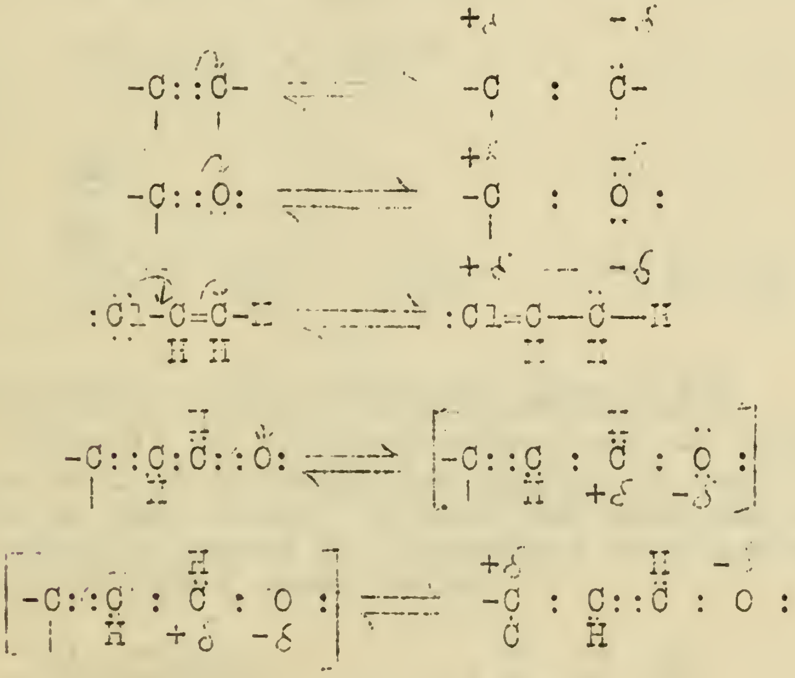
d) It is probably the most important effect operating in saturated molecules since it is brought into play at the moment of reaction and exerts its influence at the transition state. In the nitration of isobutane it must be the I_D effect which is responsible for the formation of a tertiary nitroparaffin since isobutane has no dipole moment and there are nine times as many primary hydrogen atoms as tertiary hydrogen atoms.

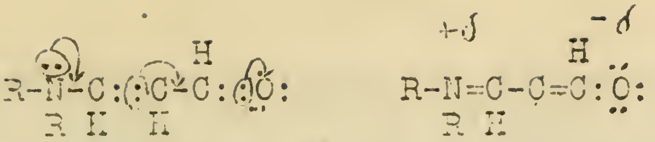


$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-H + HNO_3 \xrightarrow{100^\circ} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-NO_2 + H_2O$$

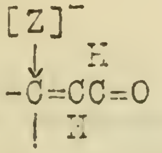
4) Characteristics of the Electromeric Effect (E)

a) The electromeric effect is a polarizability phenomenon which operates always over an unsaturated system. When a conjugated system is involved, electrons which are shared in a multiple bond with one atom frequently become shared with another by a process known as a tautomeric mechanism. This process can be relayed without disruption of the molecule.

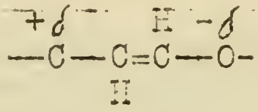


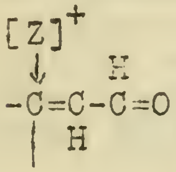


b) Inasmuch as the E effect is a polarizability phenomenon only, it serves to labilize the electronic system of the molecule. The overall result is that the energy necessary for reaction is lowered considerably by the resulting charge separation. The electromeric effect never operates in opposition to the demand of a reagent.



facilitated by





Ease of attack of $[Z]^+$ is not helped or hindered by -E of -CHO group.

c) The ease with which electromeric displacements occur can be predicted as with the inductomeric shift except that the order is reversed in going down a given group in the periodic system. Thus

+E

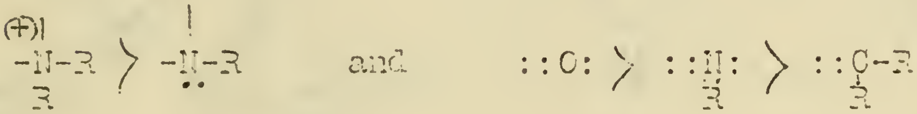
$-O^{\ominus} > OR > \overset{\oplus}{O}R_2$

$-\overset{\ominus}{\ddot{C}}- > -\overset{\ominus}{\ddot{N}}: > -\overset{\ominus}{\ddot{O}}:$

F > Cl > Br > I

OR > SR > SeR

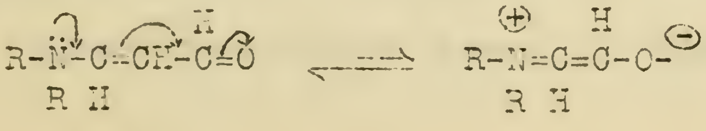
-E



$-\overset{\oplus|}{\underset{R}{N}}-R > -\overset{|}{\ddot{N}}-R$ and $::O: > ::\underset{R}{N}: > ::\underset{R}{C}-R$

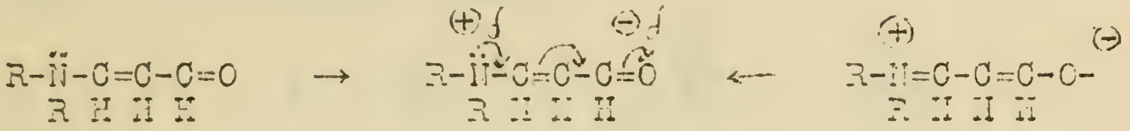
5) Characteristics of the Mesomeric Effect (M)

a) When there is an electron source and an electron sink arranged on the ends of a conjugated system in such a manner that they reinforce each other, it is clear that the resting state of the molecule cannot be accurately represented by either of the extreme formulas shown below:



I II

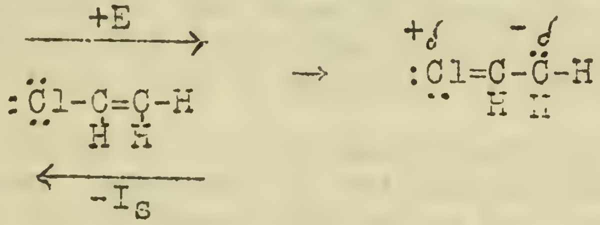
The most accurate picture of the properties of this compound is a hybrid of the two structures. This condition should not be thought of as an equilibrium between I and II but rather as a permanent resting position between the two forms.

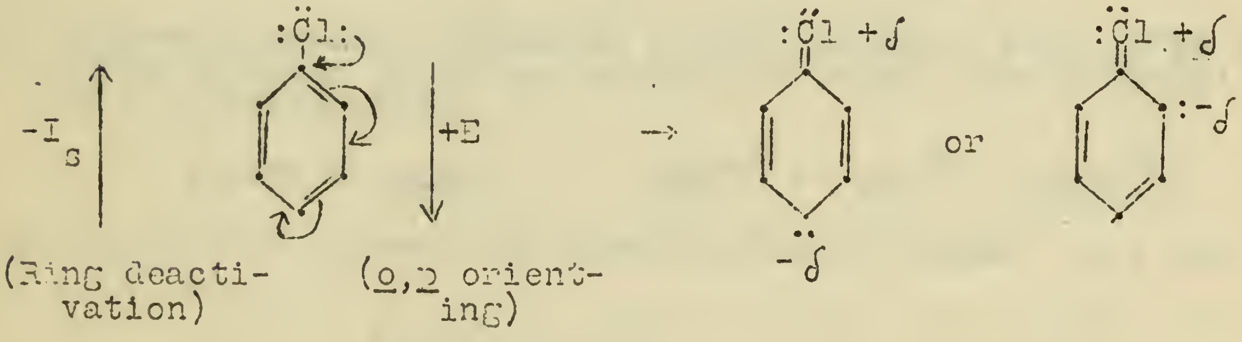


I Mesomeric State II

A molecule in this condition is said to be in a mesomeric or resonance state and the amount by which the distribution of electrons in the mesomeric state differs from I or II is a measure of the mesomeric effect (M). Since the development of charges shown is a permanent polarization effect, the mesomeric effect can hinder a reaction for which the electron distribution is unfavorable.

b) The electromeric effect (E) and the mesomeric effect (M) are the most important effects to be considered in unsaturated molecules. Whenever they can operate they will be found to outweigh either the inductive effect (I_S) or the inductomeric effect (I_D).





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1. Remick, "Electronic Interpretation of Organic Chemistry," pp. 58-59.

2. Watson, "Modern Theories of Organic Chemistry," pp. 82-105.

General: In a heterolytic cleavage of a covalent bond between two atoms X and Y, one of them (X) acquires a unit positive charge by virtue of having lost an electron which was furnished in establishing the covalent bond with Y. The other, (Y), correspondingly now carries a unit negative charge.

$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{X}} : \overset{\cdot\cdot}{\underset{\cdot\cdot}{Y}}: \rightarrow [:\overset{\cdot\cdot}{\underset{\cdot\cdot}{X}}]^{\oplus} + [:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Y}}:]^{\ominus}$$

When X is a carbon atom the ion $[:\overset{\cdot\cdot}{C}]^{\oplus}$, having only six electrons in its valence shell, is called a carbonium ion. If Y is a carbon atom, the ion $[:\overset{\cdot\cdot}{C}:]^{\ominus}$, which has an unshared electron pair, is called a carbanion. Both carbonium ions and carbanions are frequently postulated as transitory intermediates in ionic reactions.

Evidence for the Existence of Carbonium Ions: (1) Although it is the exception rather than the rule that reaction intermediates can be isolated, there can be no doubt but that in special instances carbonium ions exist.

1) Triphenylmethyl bromide dissolved in chloroform, benzene, or ethyl acetate yields a colorless non-conducting solution. In liquid sulfur dioxide its solutions are intensely yellow and are excellent conductors. The same behavior is observed in the case of hexaphenylethane. The absorption curves of the solutions in liquid SO_2 are quite similar, but different from a solution of hexaphenylethane in ether.

2) The addition of the non-electrolytes $SnCl_4$ and $AlCl_3$ to a benzene solution of triphenylmethyl chloride causes ionization as evidenced by color and conductivity.

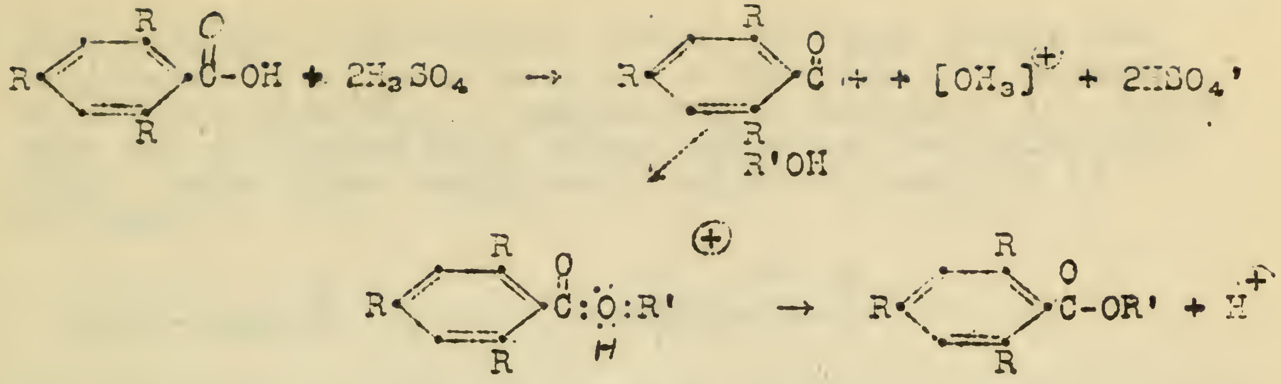
3) Triphenylcarbinol dissolved in 100% sulfuric acid gives a molar freezing point depression four times that produced by a nonelectrolyte.

$$\phi_3C\text{-}OH + 2H_2SO_4 \qquad [\phi_3C]^{\oplus} + [OH_3]^{\oplus} + 2H_2SO_4^{\ominus}$$

4) A number of colored but anhydrous perchlorates have been isolated.

$$[\phi_3C]^{+} \ [ClO_4]^{-}$$

5) o,o' Disubstituted benzoic acid produces a fourfold depression in 100% sulfuric acid and can be esterified by pouring the resulting solution into excess alcohol.



6) Aluminum chloride and aluminum bromide give conducting solutions in ethyl chloride and ethyl bromide, respectively. Transference experiments indicate that aluminum is in the anion

$$EtCl + AlCl_3 \qquad [Et]^{+} + [AlCl_4]^{-}$$

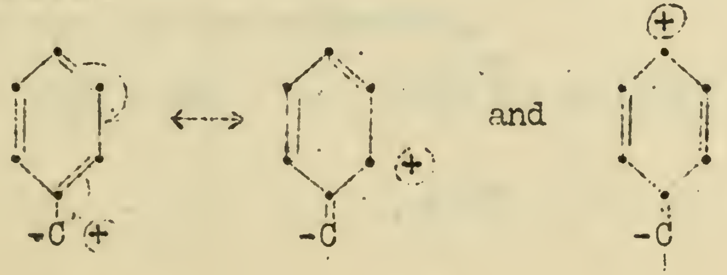
Electronic Requirements for Carbonium Ion Stability: An examination of the mechanism by which carbonium ions are formed

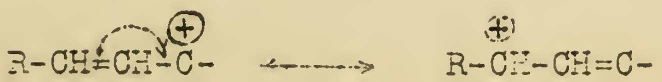
$$:\ddot{C}\,:\,\ddot{X}: \rightleftharpoons [:\ddot{C}]^{+} + [:\ddot{X}:]^{-}$$

shows that in general any agency which can feed in electrons to the carbon atom from which the electrons are lost should facilitate carbonium ion formation. Such an effect will not only aid bond breaking, but will also stabilize the carbonium ion once formed by distributing the point charge throughout the structure of the ion thereby lowering its tendency toward recombination. The following points might be considered.

1) In a saturated molecule alkyl groups (particularly methyl groups) exhibit a considerable $+I_D$ effect. The effect is cumulative so that tertiary carbonium ions are the most stable, secondary next, and primary carbonium ions most unlikely to form. Once formed, however, it is important to note that the order of reactivity is in the opposite direction. It is probably this fact which is responsible for the catalytic alkylation of isoparaffins.(2)

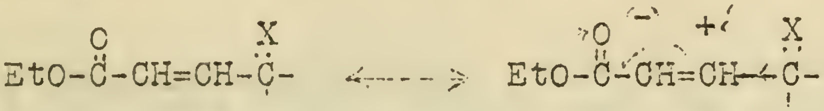
2) A phenyl group or double bond attached to the carbon atom from which the electrons are to be withdrawn enables a + E effect to operate. Consequently, such systems form carbonium ions readily.





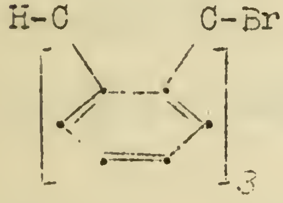
$$R\text{-}CH{=}CH\text{-}\overset{+}{C}\text{-} \longleftrightarrow R\text{-}\overset{+}{C}H\text{-}CH{=}C\text{-}$$

3) When carbonyl, carbethoxyl, nitro, or cyano groups are conjugated in a system such as in 2) there is a mesomeric effect (M) operating in opposition to carbonium ion formation and no electromeric effect which can be called into play. Under these conditions carbonium formation is unlikely.



$$\mathrm{EtO}-\overset{O}{\overset{\|}{C}}-CH=CH-\underset{|}{\overset{X}{\overset{\cdot\cdot}{C}}}- \longleftrightarrow \mathrm{EtO}-\overset{\overset{(-)}{O}}{\overset{\|}{C}}-CH=CH-\overset{X}{\underset{|}{\overset{\cdot\cdot}{C}}}-$$

4) The carbonium ion must be able to assume a planar configuration. If this is prevented no carbonium ion will form.



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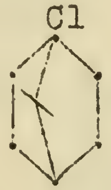


$\xrightarrow[\text{alc.}]{AgNO_3}$ No reaction

1-Bromo-triptycene

1-Chloroapo-camphane

Reactions Which Frequently Form Carbonium Ions:

1) Addition of acids to unsaturated compounds.

(a) Carbonyl compounds:

$$-\underset{|}{C}::\underset{\cdot\cdot}{O}: + [H]^{(+)} \longrightarrow [-\underset{|}{C}:\overset{\oplus}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}}:H] \longleftrightarrow [-\underset{|}{\overset{\oplus}{C}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:H]$$

(b) Olefins:

$$-\underset{|}{C}=\underset{|}{C}- \longrightarrow -\underset{|}{\overset{\oplus}{C}}-\underset{|}{\overset{\ominus}{C}}- + H^{(+)} \longrightarrow [-\underset{|}{\overset{\oplus}{C}}-\underset{|}{\overset{H}{C}}-]$$

2) Addition of acids to saturated molecules which can later lose water or alcohol.

(a) Alcohols:

$$:\overset{|}{\underset{|}{C}}-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}H + [H]^{+} \longrightarrow [-\overset{|}{\underset{|}{C}}-\overset{\overset{+}{H}}{\underset{\cdot\cdot}{O}}H] \longrightarrow [-\overset{|}{\underset{|}{C}}\oplus] + :\overset{H}{\underset{\cdot\cdot}{O}}:H$$

(b) Ethers:

$$-\overset{|}{\underset{|}{C}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:R + [H]^{\oplus} \longrightarrow [-\overset{|}{\underset{|}{C}}:\overset{\overset{\oplus}{H}}{\underset{\cdot\cdot}{O}}:R] \longrightarrow [-\overset{|}{\underset{|}{C}}\oplus] + :\overset{H}{\underset{\cdot\cdot}{O}}:R$$

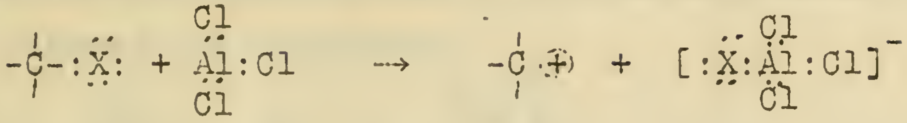
3) Decomposition of azo compounds,

$$-\overset{|}{\underset{|}{C}}-NH_2 + HONO + HCl \longrightarrow [(-\overset{|\,+}{\underset{|}{C}}:N:::N:)(Cl)^{-}]$$

$$\downarrow$$

$$[-\overset{|}{\underset{|}{C}}\oplus] + :N:::N: + Cl^{-}$$

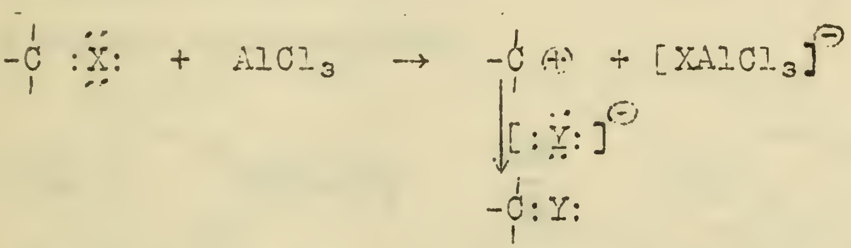
4) Coordination of halides with metal salts.



also BX_3, $ZnCl_2$, $SnCl_4$

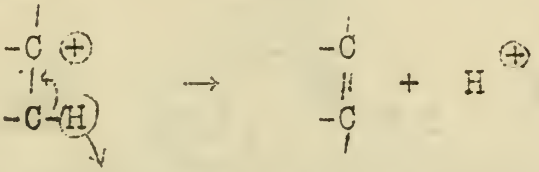
Reactions of Carbonium Ions: After a carbonium ion has been formed, its reactions depend largely upon the structure of the ion, the nature of the groups attached to it, and to the medium in which the reaction is being carried out. There are three courses of reaction open to it.

1) Recombination with another electron rich species:



This mode of reaction is characteristic of solvolytic and Sn_1 reactions. It will be discussed under "Displacement Reactions."

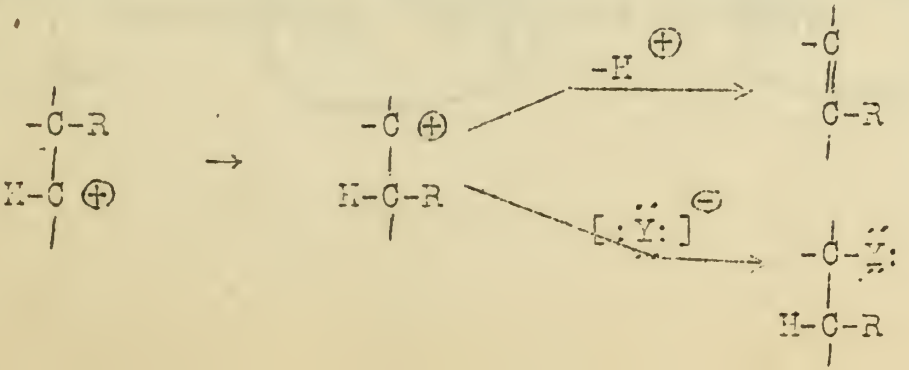
2) Elimination of a proton from an α carbon atom to form an olefin.



This is the mechanism of acid dehydration and will be discussed under "Elimination Reactions."

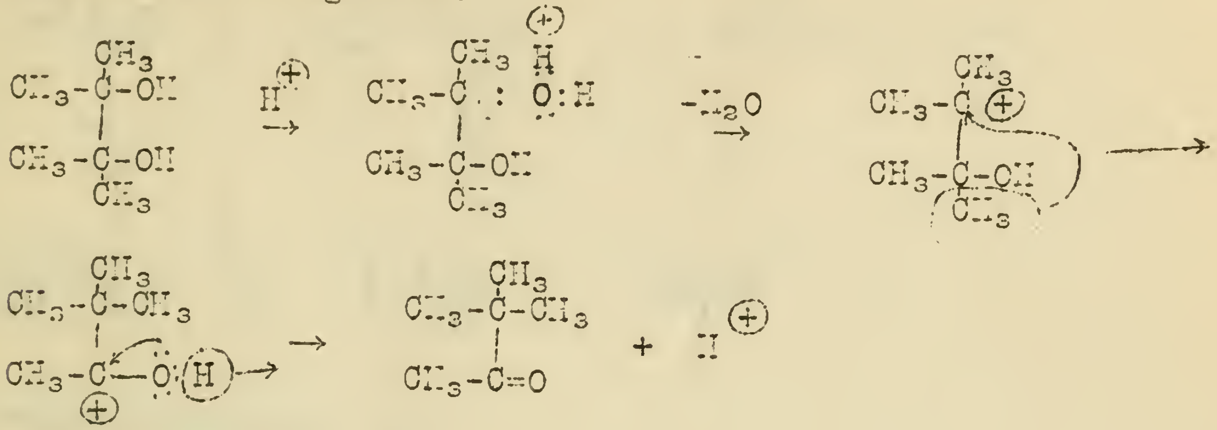
3) Molecular Rearrangement:

The last possibility for carbonium ion reaction is that of rearrangement. Carbonium ion rearrangements are characterized by the shift of an alkyl group or a hydrogen atom - together with an electron pair - from an α carbon atom. A new carbonium ion is thus formed with the charge now on what was once an α carbon atom and subsequent reaction may proceed by 1) or 2). This principle was first recognized by Whitmore(3) and can be illustrated as follows:

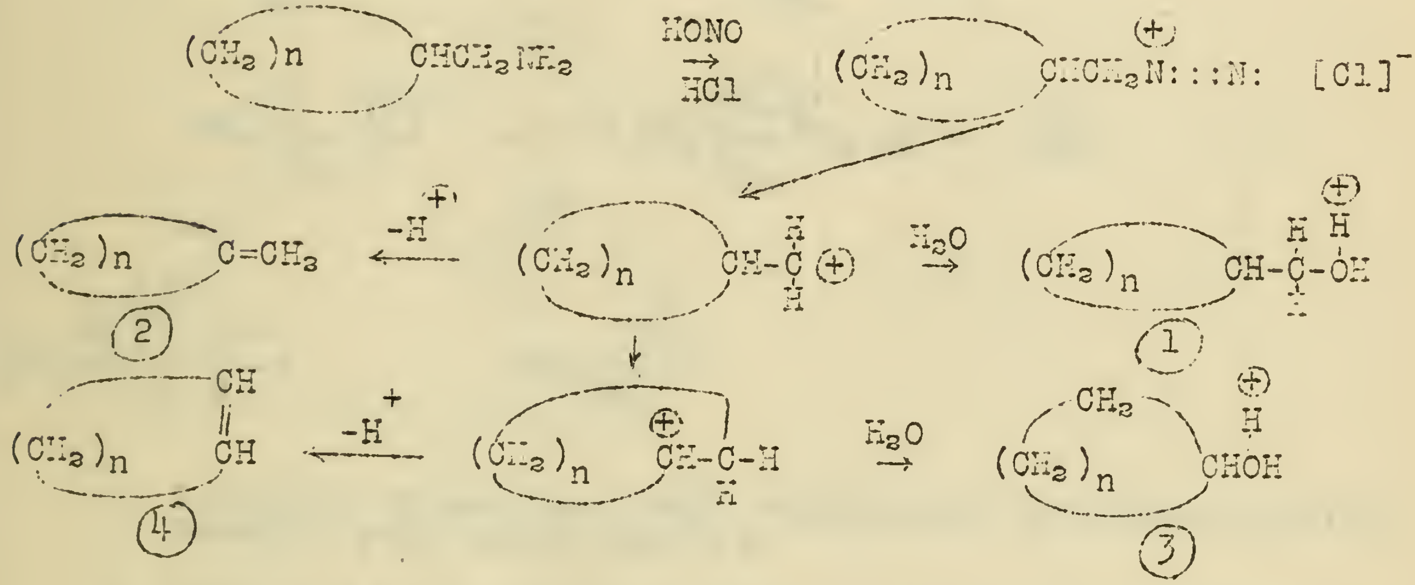


Examples of Molecular Rearrangements Involving Carbonium Ions:

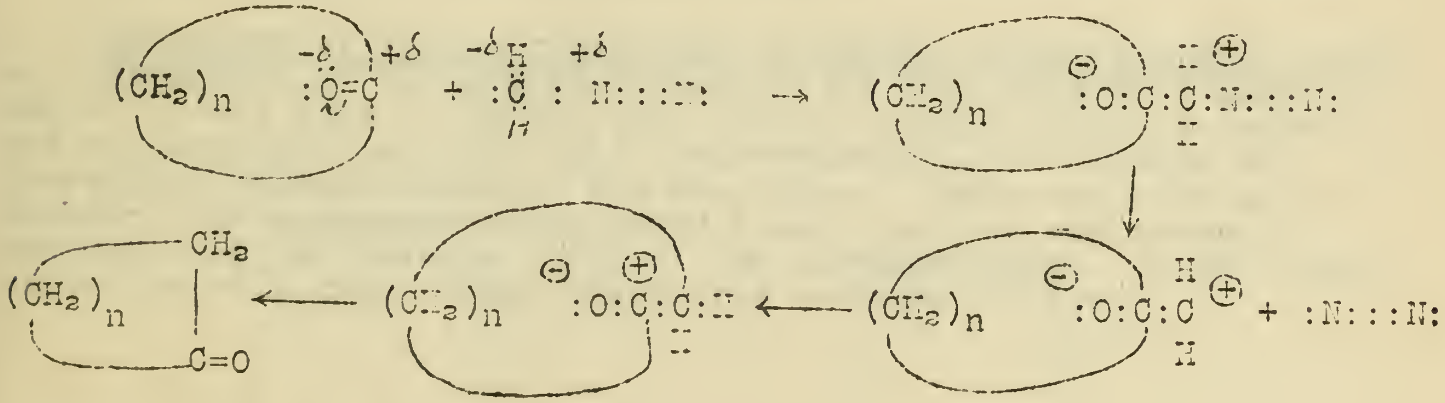
1. Pinacol Rearrangement.



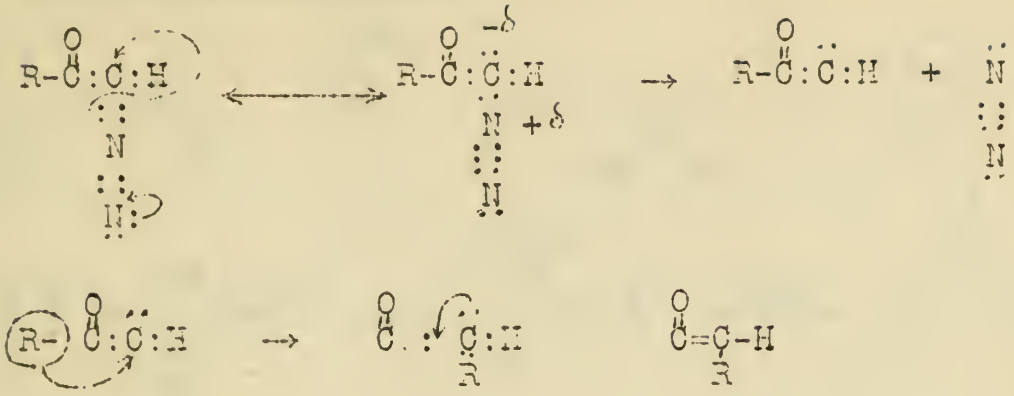
2. Demjanow Rearrangement.



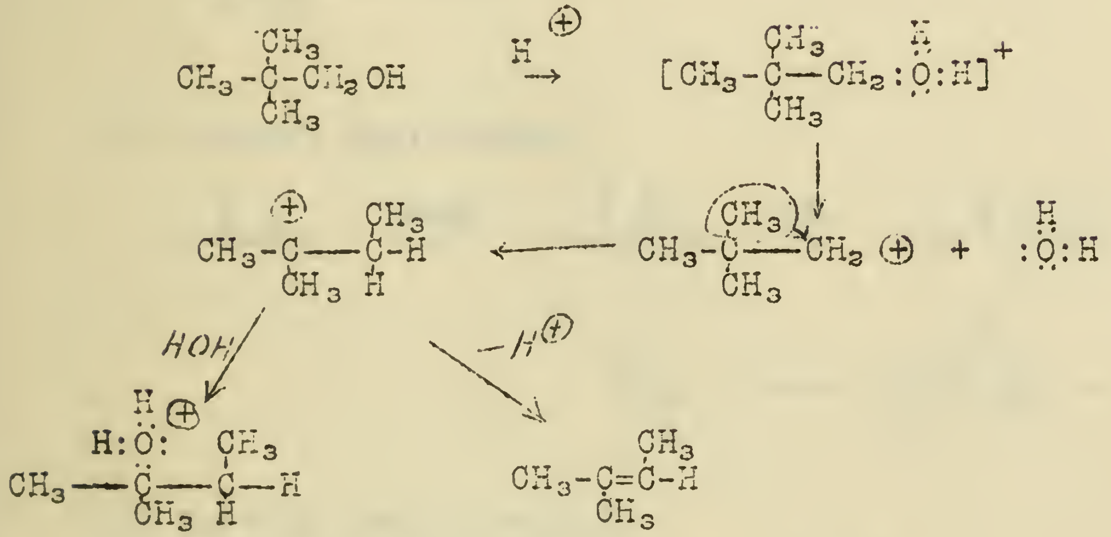
3. Ring Expansion with Diazomethane.



4) Wolff Rearrangement.



5) Wagner-Meerwein.

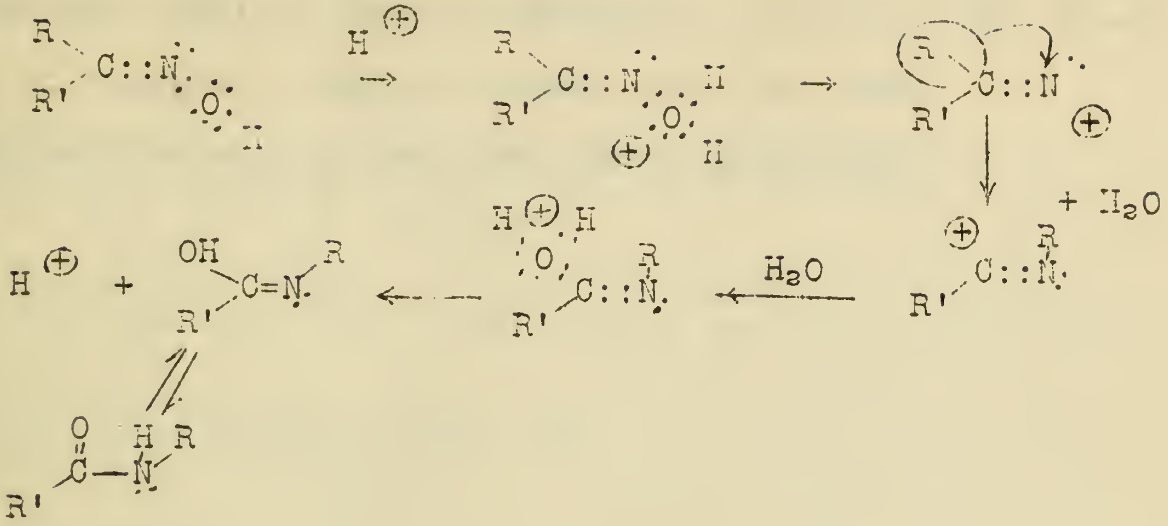


6) Formation of branched-chain products in the Friedel-Crafts reaction with normal halides.

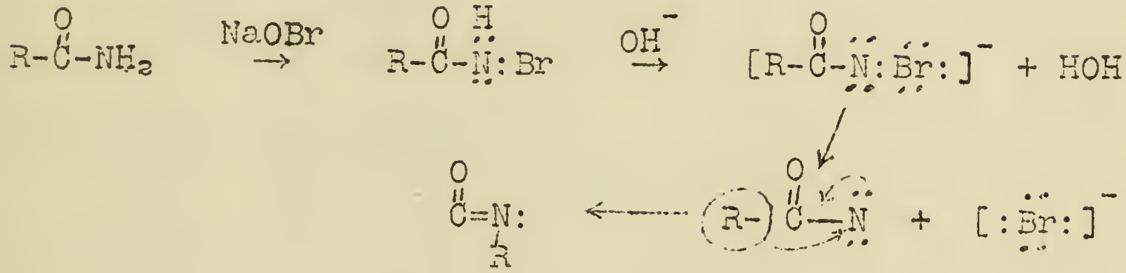
7) Formation of anomolous products in isoparaffin alkylation.

Extension of the Carbonium Ion Principle to the Nitrogen Atom: An examination of the driving force of the rearrangements shown above reveals that it is not the positive charge which is responsible for reaction (cf. the Wolff rearrangement), but rather an incomplete valence shell of six electrons. There are a number of similar rearrangements which occur when a pair of electrons is removed from the valence shell of the nitrogen atom. In all cases migration of a group takes place from an adjacent atom.

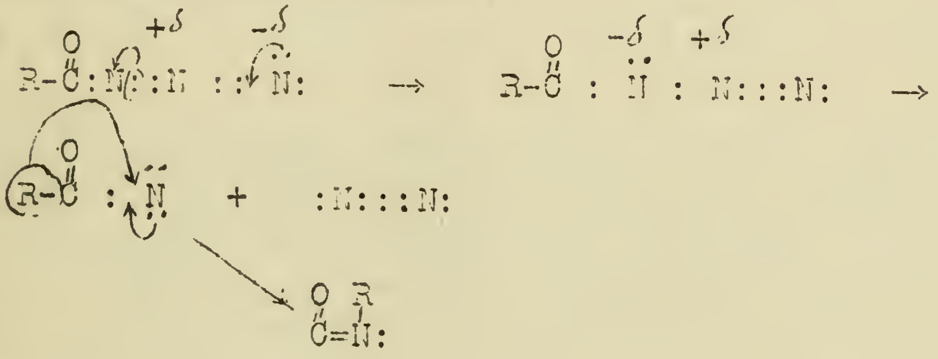
1) Beckmann Rearrangement.



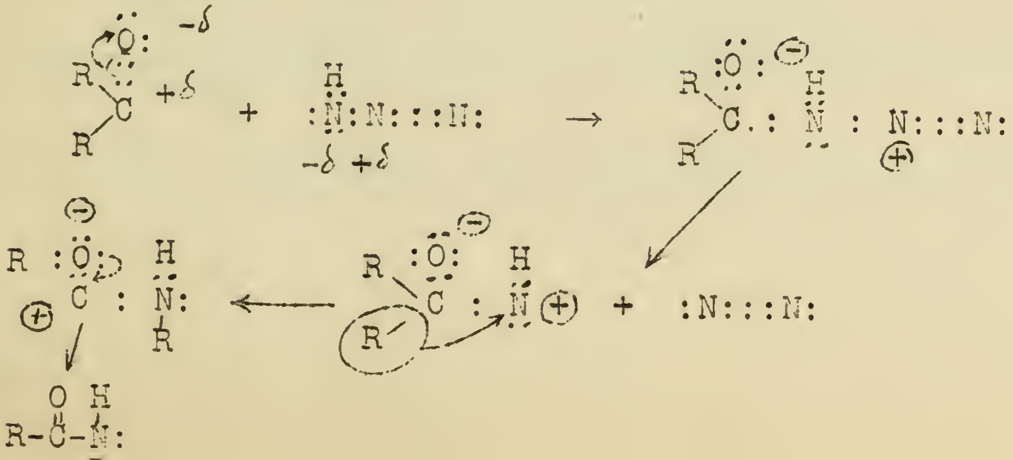
2) Hofmann Degradation.


NaOBr
OH⁻
+ HOH

3) Curtius Rearrangement.



4) Schmidt Reaction.



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(1) Hammett, Physical Organic Chemistry, pp. 53-56, 65, 291-328.

(2) J. H. Brewster, Organic Seminar, Jan. 10, 1947.

(3) Whitmore et al., J. Am. Chem. Soc., 1932-1938.

General.--Probably the most important type of reaction in organic chemistry is the displacement reaction.

$$A + BC \rightarrow AB + C$$

The prevalence of this kind of reaction must mean that the energy barriers to be surmounted are lower for displacements as a group than for other types of reactions.

Fundamentally there are two different modes whereby such transformations may occur. They depend upon the electrical character of A.

Nucleophilic Substitution (S_n)

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}: + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}: \rightarrow :\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:B: + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:$$

(A is nucleus-seeking. Characteristic of reagents having completely filled valence shells.)

$$[H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:]^{\ominus} + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:Cl: \rightarrow HO:\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}: + [:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:]^{\ominus}$$

Electrophilic Substitution (S_E)

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}} + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:C: \rightarrow :\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:B: + \underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:$$

(A is electron-seeking. Characteristic of reagents having incomplete valence shells.)

$$Cl:\underset{Cl}{\overset{Cl}{Al}} + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}: \rightarrow [Cl:\underset{Cl}{\overset{Cl}{Al}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:]^{-} + [\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:]^{+}$$

Duality of the Mechanism of Nucleophilic Substitution.--In many instances of nucleophilic substitution - say the alkaline hydrolysis of alkyl halides - it is found that if a homologous series is arranged in the order of increasing release, ($+I_D$ or $+I_S$), the rate of reaction decreases in proceeding from one member to the next and is proportional to the concentration of alkyl halide and hydroxyl ion. Eventually the rate passes thru a minimum where no such simple mathematical relationship obtains and finally it increases again. With these members of the series the rate of reaction is dependent only upon the concentration of the alkyl halide. It is independent of the concentration of the attacking nucleophilic reagent (hydroxyl ion).

The simplest explanation for this phenomenon is to assume that nucleophilic substitution can occur in either of two ways.

A.) $:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}: + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:C: \rightarrow :\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}: + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:$

$$\text{rate} = k\,[:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:]\,[:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:]$$

Substitution - nucleophilic - 2nd order $\therefore Sn_2$

[illegible]

[illegible]

The advantage of this type of [illegible] that [illegible] to be [illegible] than the other types of [illegible].

Fundamentally there are two different [illegible] transformations are [illegible] point of A.

[illegible] (..)

[illegible]

(A is [illegible])

[illegible]

[illegible] (..)

[illegible]

[illegible]

[illegible]

[illegible]

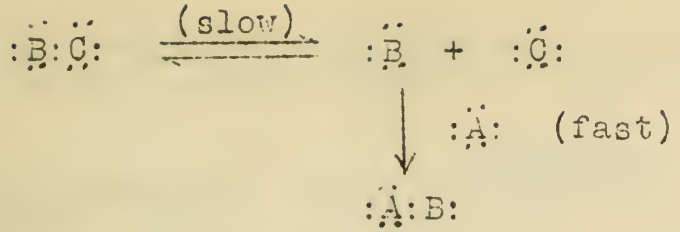
The simplest [illegible]

A.) [illegible]

where [illegible]

Transformation [illegible]

B.)



rate = k [:B:C:]

Substitution - nucleophilic - 1st order ∴ Sn_1

This hypothesis at least correlates the facts of the alkaline hydrolysis of alkyl halides since electron release would hinder the approach of the negatively charged hydroxyl group (Sn_2) and would favor ionization (Sn_1). While the postulation of a carbonium ion as an intermediate in an Sn_1 reaction presents some difficulties;(1) nevertheless it must be admitted that all correlation of electrical effects and reactivity agree well with such an assumption.

It is clear that in order to predict the effect of structure on reactivity, the mechanism of nucleophilic substitution must be known since electron release hinders Sn_2 but aids Sn_1.

Structural Factors Influencing Sn_1 and Sn_2.--

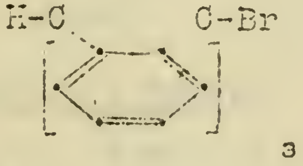
1.) Steric Hindrance:

In the hydrolysis of alkyl halides by hydroxyl ion, the rate of the Sn_2 reaction decreases rapidly in the series shown until in the case of neopentyl halides it

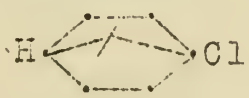
$CH_3CH_2CH_2-$, $(CH_3)_2CHCH_2-$, $(CH_3)_3CCH_2-$

is almost negligible. This is due to the fact that the *t*-butyl group protects the methylene carbon atom from a backside attack by the hydroxyl group. (See the Stereochemistry of the Displacement Reaction.)

In this connection it is interesting to note that 1-chloroapocamphane and 1-bromotriptycene are completely inert to Sn_2 and Sn_1 reactions.

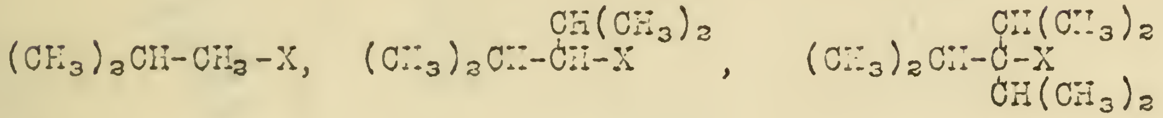


and



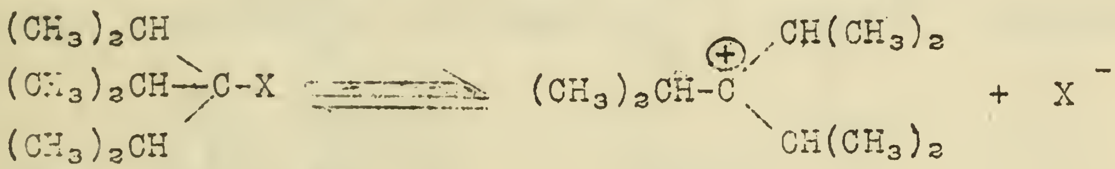
1-bromotriptycene 1-chloroapocamphane

Sn$_1$ reactions are profoundly influenced by the introduction of a certain maximum number of alkyl groups.(2) In the series



$$(CH_3)_2CH-CH_2-X, \quad (CH_3)_2CH-\overset{CH(CH_3)_2}{CH}-X, \quad (CH_3)_2CH-\underset{CH(CH_3)_2}{\overset{CH(CH_3)_2}{C}}-X$$

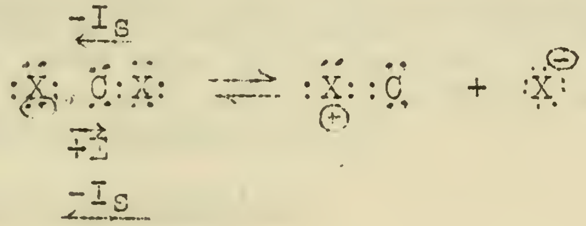
An enormous increase in the reactivity of the last compound by an Sn$_1$ mechanism is observed. Presumably this is due to a pressure the isopropyl groups have on each other when the valence bonds of the central carbon atom are forced into a tetrahydral configuration ("B strain").(3) This strain can be relieved when the central carbon atom has only six electrons about it and so the equilibrium shown below is forced to the right.



2.) Polyhalogen Compounds:

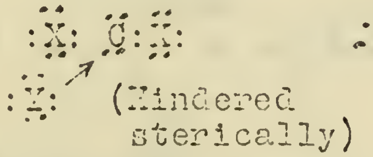
a.) When halogen atoms are attached to the same carbon atom

Sn$_1$:



∴ Helped

Sn$_2$:



∴ Hindered

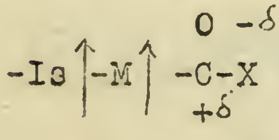
b.) When halogen atoms are separated by two carbon atoms

Sn$_1$: $\overset{-I_s}{\longleftarrow}$

$Cl \leftarrow C \leftarrow C-Cl$ ∴ Hindered

Sn$_2$: Helped

3.) Carbonyl Group:

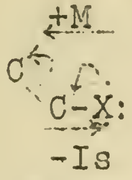


$$-I_s \uparrow -M \uparrow \underset{+\delta}{\overset{O\ -\delta}{-C}}-X$$

Sn$_1$: Hindered

Sn$_2$: Helped

4.) Vinyl and Aryl Groups:

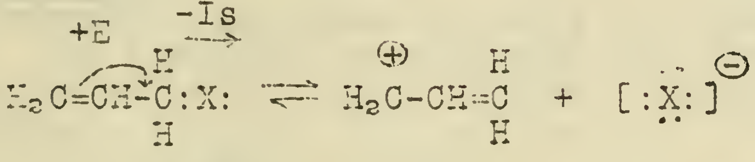


Sn_1: Hindered

Sn_2: Hindered

5.) Allyl Group:

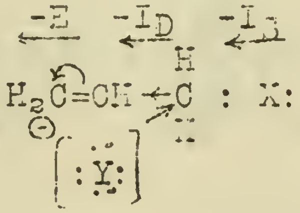
Sn_1:



$H_2C{=}CH{-}CH_2{:}X: \rightleftharpoons H_2\overset{\oplus}{C}{-}CH{=}CH_2 + [:X:]^{\ominus}$

Helped

Sn_2:

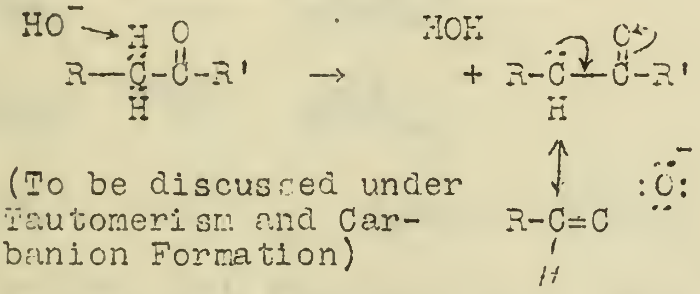


$H_2C{=}CH{-}CH_2 : X: \quad \overset{\ominus}{[:Y:]}$

Helped

Nucleophilic Displacements on Other Atoms than Carbon.--While all of the nucleophilic substitution reactions which have been discussed so far have been on carbon atoms, it is nevertheless important to realize that many other important reactions are displacements on hydrogen or halogen atoms.

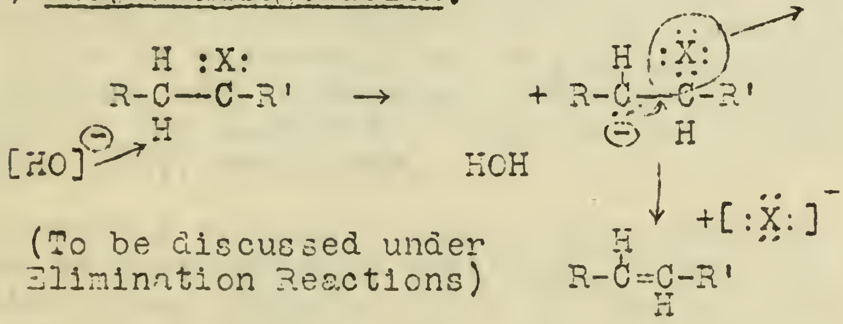
1.) Base Catalyzed Enolization:



$HO^- + R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}R' \rightarrow HOH + R{-}\overset{..}{C}H{-}\overset{O}{\overset{\|}{C}}{-}R' \leftrightarrow R{-}CH{=}C{-}R'(:\ddot{O}:^-)$

(To be discussed under Tautomerism and Carbanion Formation)

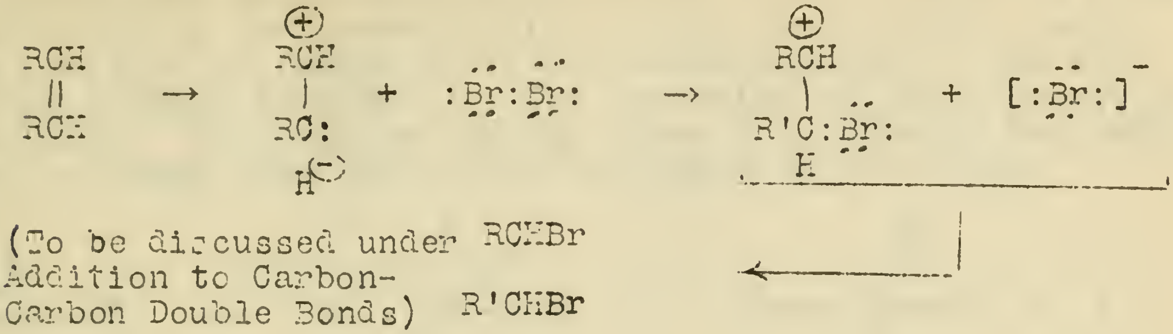
2.) Dehydrohalogenation:



$R{-}CH_2{-}CHX{-}R' + [HO]^{\ominus} \rightarrow HOH + R{-}\overset{\ominus}{C}H{-}CHX{-}R' \rightarrow R{-}CH{=}CH{-}R' + [:X:]^-$

(To be discussed under Elimination Reactions)

3.) Addition of Halogens to Olefins:

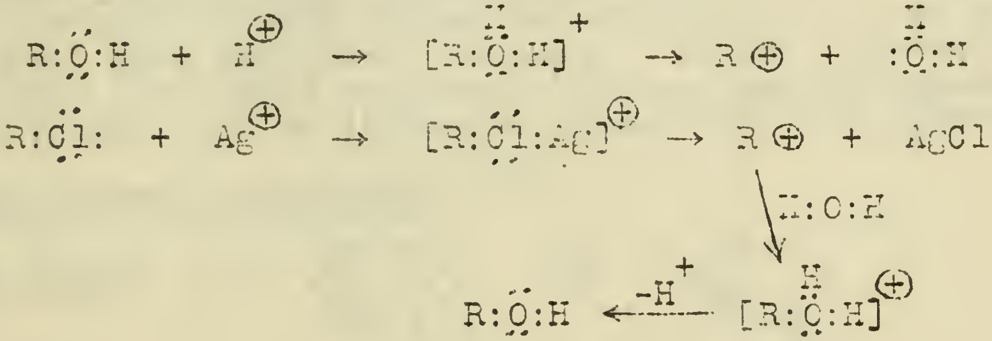


$$\begin{matrix}\mathrm{RCH}\\ \Vert\\ \mathrm{RCH}\end{matrix} \rightarrow \begin{matrix}\overset{\oplus}{\mathrm{RCH}}\\ |\\ \mathrm{R\ddot{C}{:}}\\ \mathrm{H}^{\ominus}\end{matrix} + {:}\ddot{\mathrm{Br}}{:}\ddot{\mathrm{Br}}{:} \rightarrow \begin{matrix}\overset{\oplus}{\mathrm{RCH}}\\ |\\ \mathrm{R'C{:}\ddot{Br}{:}}\\ \mathrm{H}\end{matrix} + [{:}\ddot{\mathrm{Br}}{:}]^{-}$$

(To be discussed under Addition to Carbon-Carbon Double Bonds)

$$\begin{matrix}\mathrm{RCHBr}\\ \mathrm{R'CHBr}\end{matrix}$$

$\underline{Sn_1}$ Displacements.--There are a number of metathetical reactions which apparently take place by means of a preliminary electrophilic attack. The formation of carbonium ions from alcohols or ethers and the hydrolysis of alkyl halides by mercuric or silver ions are examples.

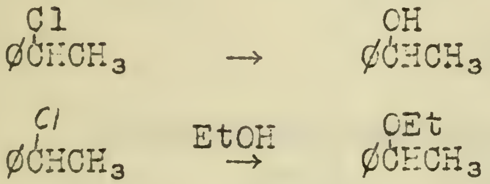


$$\mathrm{R{:}\ddot{O}{:}H} + \mathrm{H}^{\oplus} \rightarrow [\mathrm{R{:}\ddot{O}{:}H}]^{+} \rightarrow \mathrm{R}^{\oplus} + \mathrm{{:}\ddot{O}{:}H}$$

$$\mathrm{R{:}\ddot{Cl}{:}} + \mathrm{Ag}^{\oplus} \rightarrow [\mathrm{R{:}\ddot{Cl}{:}Ag}]^{\oplus} \rightarrow \mathrm{R}^{\oplus} + \mathrm{AgCl}$$

$$\mathrm{R}^{\oplus} \xrightarrow{\mathrm{H{:}O{:}H}} [\mathrm{R{:}\overset{H}{\ddot{O}}{:}H}]^{\oplus} \xrightarrow{-\mathrm{H}^{+}} \mathrm{R{:}\ddot{O}{:}H}$$

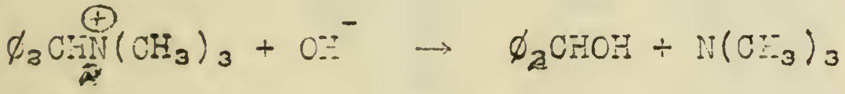
Similarly there are a number of hydrolysis reactions the rate of which is always independent of base.



$$\mathrm{\phi\overset{Cl}{C}HCH_3} \rightarrow \mathrm{\phi\overset{OH}{C}HCH_3}$$

$$\mathrm{\phi\overset{Cl}{C}HCH_3} \xrightarrow{\mathrm{EtOH}} \mathrm{\phi\overset{OEt}{C}HCH_3}$$

Independent of OH^- or OEt^-

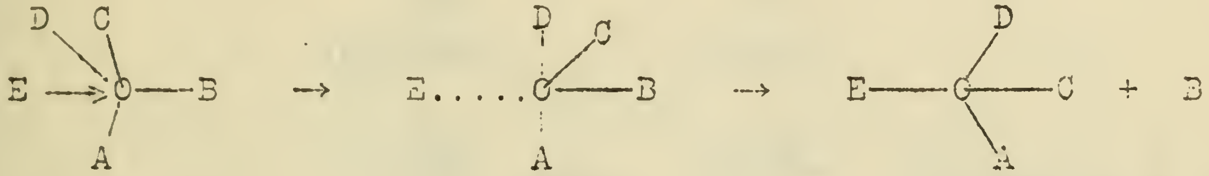


$$\phi_2\mathrm{CH}\overset{\oplus}{\mathrm{N}}(\mathrm{CH_3})_3 + \mathrm{OH}^- \rightarrow \phi_2\mathrm{CHOH} + \mathrm{N(CH_3)_3}$$

It is striking that the solvents in which this kind of reaction occurs are alcohols, sulfur dioxide, water, and carboxylic acids. These are the solvents which favor the ionization of triphenylmethyl chloride presumably by an electrophilic attack (solvation) on the halide. It is assumed, therefore, that it is the incipient solvation of the halide ion which is the driving force of the solvolytic (Sn_1) reactions.

Although a carbonium ion is postulated for this mechanism, it can have no true separate existence. With the exception of certain well-known cases (halogen acids and bromohydrins) the Sn_1 reaction of an asymmetric carbon-atom leads to inversion as does the Sn_2 reaction. In the Sn_2 reaction, however, racemization is slight while it is large in the Sn_1 reaction. This fact alone is often used as a criterion of Sn_1 and Sn_2 reactions.

Stereochemistry of Sn$_2$ Reactions.--It may now be stated that every displacement on an asymmetric carbon atom the rate of which is proportional to the concentration of the nucleophilic ion or molecule involves an inversion of the configuration of the asymmetric atom (Walden Inversion). The mechanism of this process is outlined below. The behavior of the three C-R linkages has been described as being like the ribs of an umbrella in a gale.

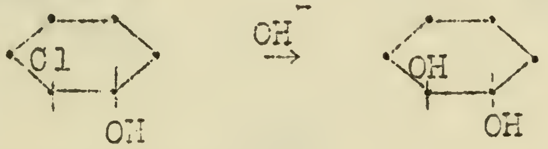


d series (Transition State) l series

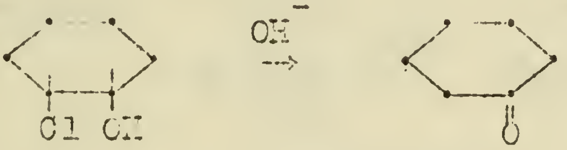
"Anomolous" Displacement Reactions.--There are a number of displacement reactions which appear to contradict some of the principles which have just been discussed. Closer inspection, however, reveals that these reactions involve two displacements with the end result that no inversion appears to have occurred.

1.) Cyclohexene Chlorohydrin (4)

The facts: A.)

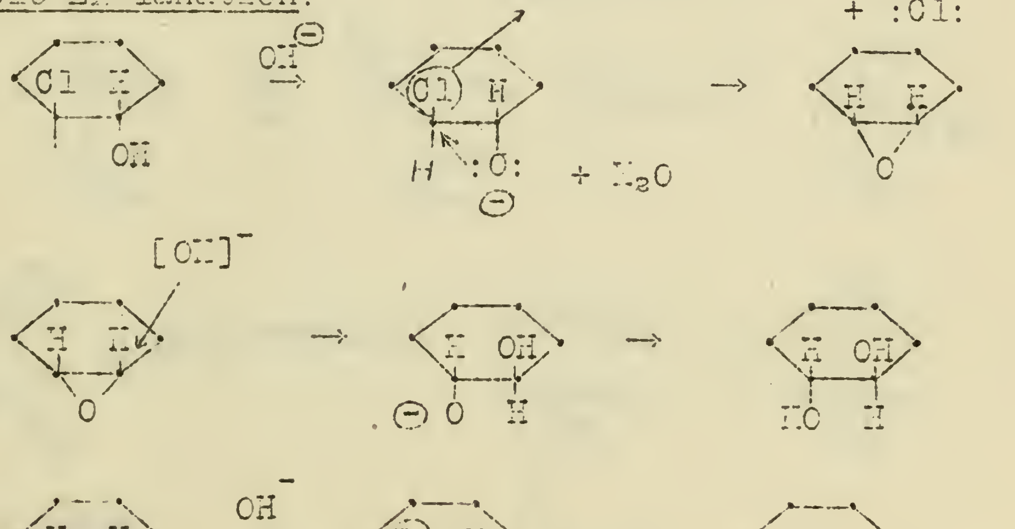

Cl
OH
OH^-
OH
OH

B.)

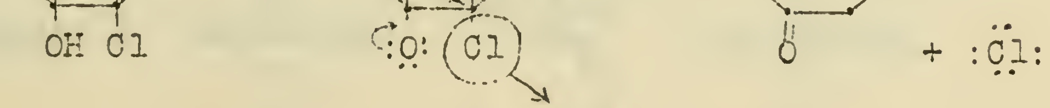


Possible Explanation:

A.)

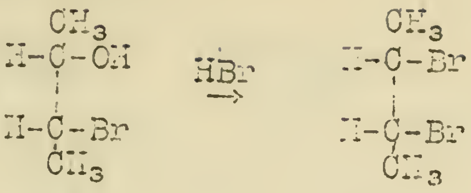

Cl H
OH
$OH^{\ominus}$
Cl H
H :O:
+ H$_2$O
+ :Cl:
H H
O
[OH]$^-$
H H
O
H OH
O H
H OH
HO H

B.)


H H
OH Cl
OH^-
H H
:O: Cl
O
+ :Cl:

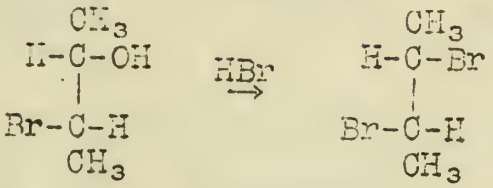
2.) Bromohydrins(5)

The facts:


CH3
H-C-OH
H-C-Br
CH3
HBr
CH3
H-C-Br
H-C-Br
CH3

(erythro) (meso)

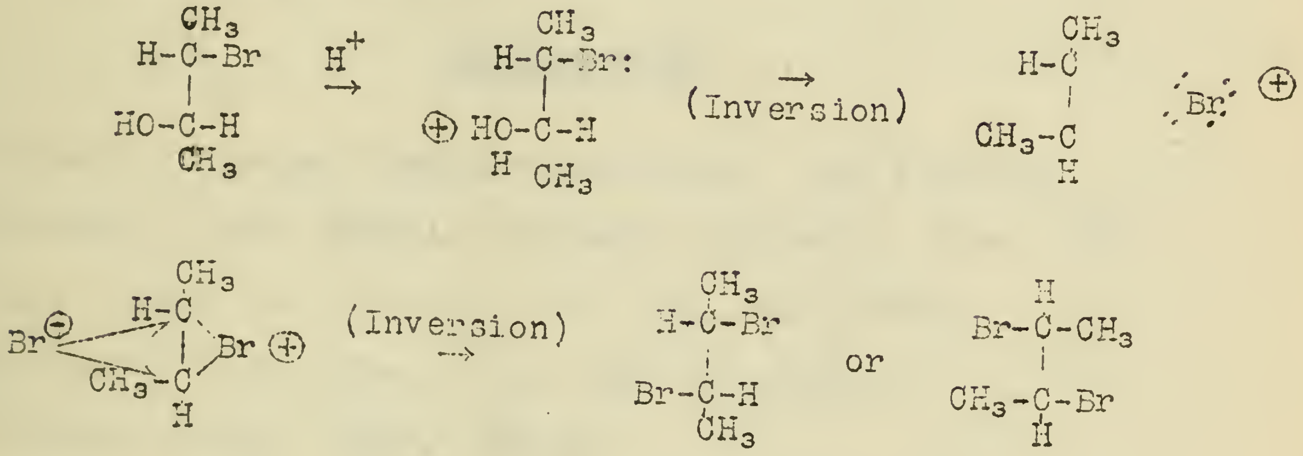
(Retention of Configuration = 100%)


CH3
H-C-OH
Br-C-H
CH3
HBr
CH3
H-C-Br
Br-C-H
CH3

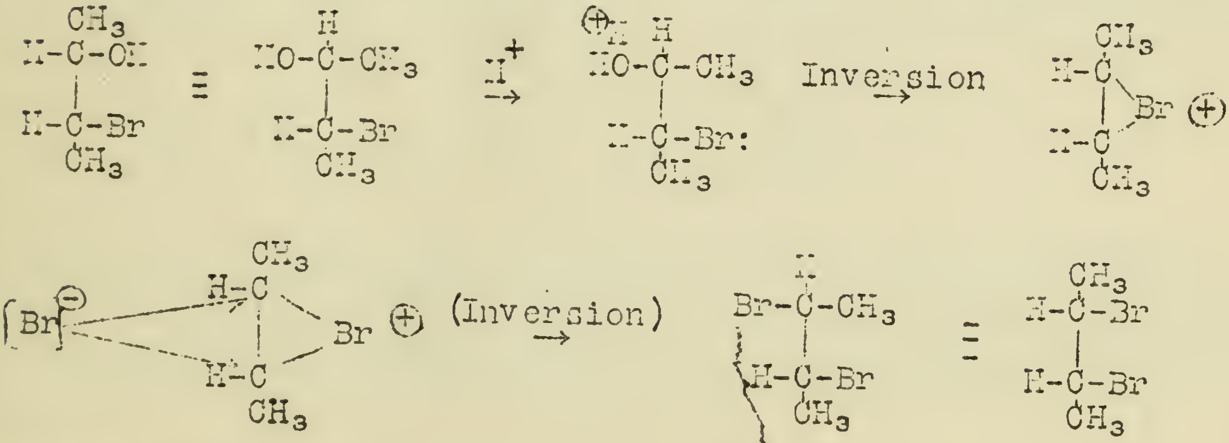
(threo) (dl)

(Retention of Configuration = 100%)

Possible Explanation:

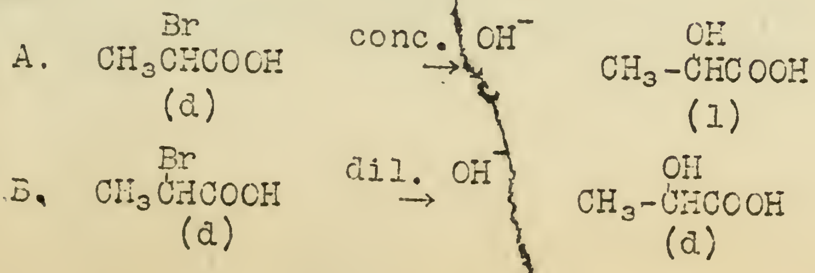

H+
(Inversion)
Br
or

(Identical)


≡
H+
Inversion
(Inversion)
≡

3.) Halogen Acids:

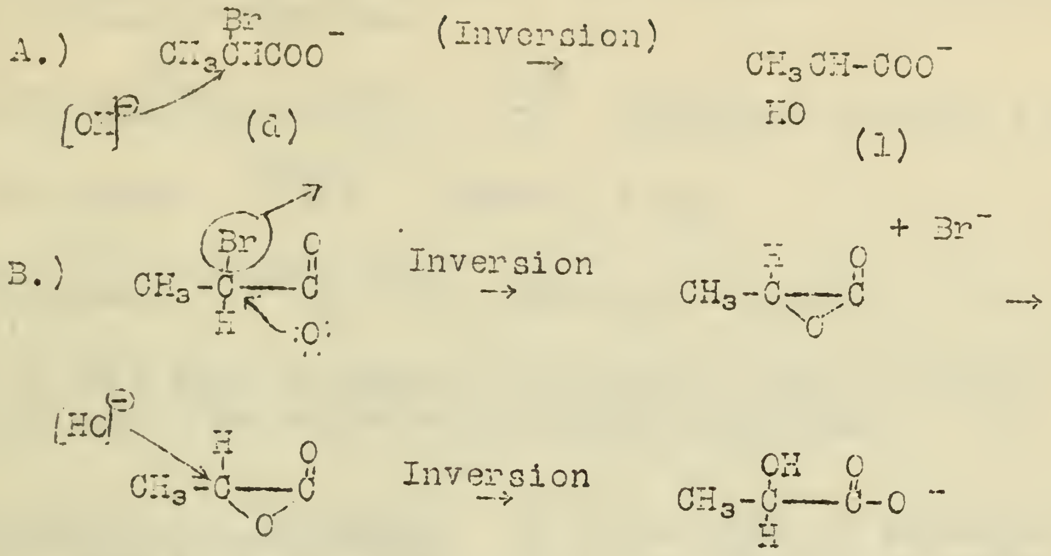
The facts:



A. $\overset{Br}{CH_3CHCOOH}$ (d) $\xrightarrow{conc.\ OH^-}$ $CH_3-\overset{OH}{C}HCOOH$ (l)

B. $CH_3\overset{Br}{C}HCOOH$ (d) $\xrightarrow{dil.\ OH^-}$ $CH_3-\overset{OH}{C}HCOOH$ (d)

Possible Explanation:


A.)
(Inversion)
(d)
(l)
B.)
Inversion
+ Br⁻
Inversion

Bibliography

(1) Hammett, "Physical Organic Chemistry," pp. 171-173.

(2) Bartlett, Tenth Organic Chemistry Symposium, June, 1947.

(3) H. C. Brown, J. Am. Chem. Soc., 66, 441 (1944).

(4) Bartlett, J. Am. Chem. Soc., 57, 224 (1935).

(5) Winstein et al., ibid., 64-68.

(6) Cowdrey, Hughes, and Ingold, J. Chem. Soc., 1243 (1938).

In spite of the differences in structure and conditions necessary for carrying out the reactions, the following transformations proceed by similar mechanisms.

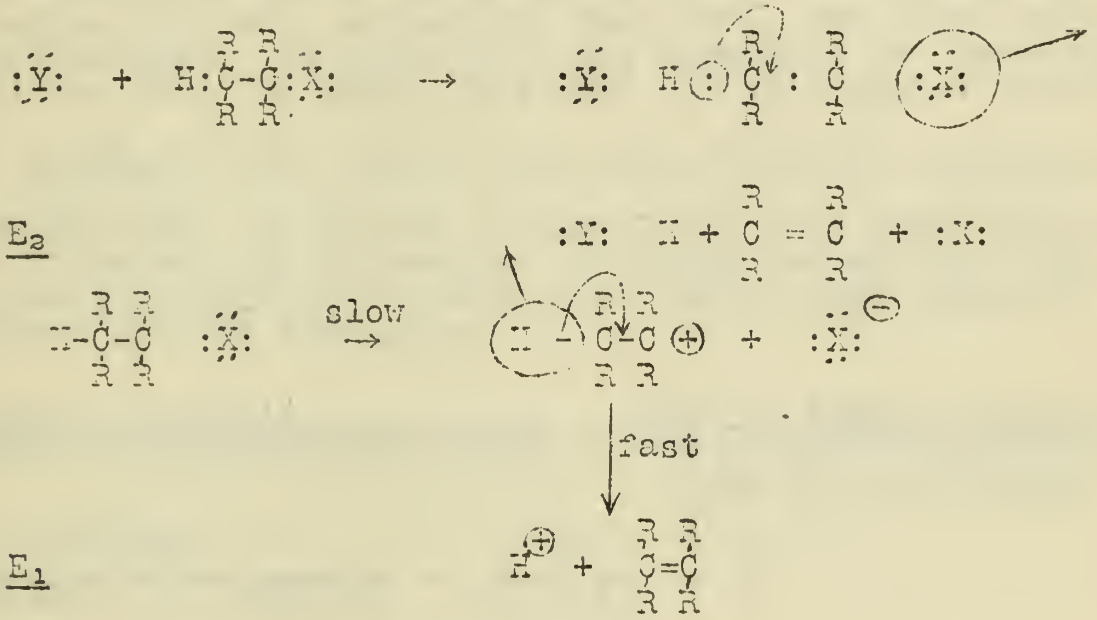
1.) $[RCH_2CH_2\overset{\oplus}{N}(CH_3)_3][I]^{\ominus} \xrightarrow[\Delta]{Ag_2O} RCH{=}CH_2 + (CH_3)_3N + H_2O + AgI$

2.) $RCH_2CH_2OH \xrightarrow[\Delta]{H_2SO_4} RCH{=}CH_2 + H_2O$

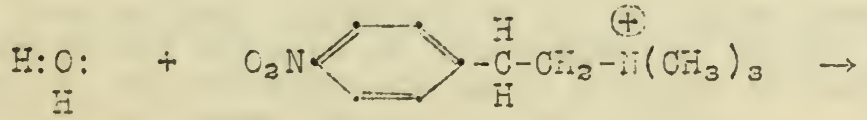
3.) $RCH_2CH_2Br \xrightarrow[\Delta]{KOH + Alc.} RCH{=}CH_2$

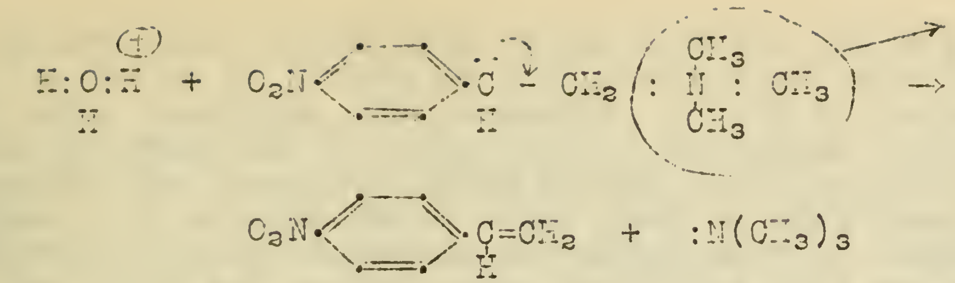
Reactions of this kind in which a molecule of water, alcohol, or acid are split out are called elimination reactions.

Mechanism of the Reactions: As in the case of substitution, the reaction occurs in two kinetically distinguishable paths. One of them is a bimolecular mechanism (E_2) in which the rate of reaction is dependent upon both the concentration of attacking reagent and the organic molecule while the other (E_1) is independent of the concentration of the attacking reagent.



Here again first order kinetics do not necessarily indicate an E_1 mechanism. The quaternary salt of dimethyl-β-p-nitrophenyl ethylamine is first order in aqueous solution. Nevertheless the reaction undoubtedly occurs by an E_2 mechanism since a large increase in speed is observed when a base stronger than water is present.





Examination of the mechanisms E_1 and E_2 reveals that they are closely related to Sn_1 and Sn_2. In fact, E_1 and Sn_1 involve the same species as an intermediate while Sn_2 and E_2 differ only in that displacement occurs at a carbon atom in one case (Sn_2) and at a hydrogen atom in the other (E_1). Consequently, in reactions of this type it is to be expected that there will be a competition among E_1, E_2, Sn_1, and Sn_2. The following discussion, therefore, will consider some of the factors which influence the course reactions of this kind will take.

Factors Influencing the Course of E and S Reactions:

1.) *Concentration of Nucleophilic Reagents.*--By definition the first order reactions must be independent of the concentration of the nucleophilic reagent. At low pH, therefore, the first order reactions predominate. Assuming that the carbonium ion decomposes before collision with the anion, the ratio of elimination to substitution, or $\frac{E_1}{E_1 + S_1}$, will depend only upon structural consideration of the carbonium ion. At higher pH when the second order reactions become more important the proportion of olefin formed will again be constant since the ratio of products will depend upon the ratio of the respective rates of formation.

$$\frac{\text{am't. of olefin}}{\text{am't of olefin + am't of substitution}} = \frac{\text{rate of olefin formation}}{\text{rate of olefin formation + rate of substitution}} =$$

$$\frac{k_E\,[RX][OH]}{k_E\,[RX][CH] + k_s\,[RX][CH]} = \frac{k_E}{k_E + K_s} = K$$

It is clear therefore that changes in the concentration of the attacking reagent can shift the mechanism towards either first order or second order reactions, but that within the same reaction path the ratio of products is independent of the concentration of the attacking reagent.

An interesting illustration of the importance of reaction order in comparing the effects of concentration can be illustrated by reference to the controversy as to whether secondary or tertiary halides give a larger proportion of olefins.

[illegible]

Factors Influencing the Course of the Reactions:

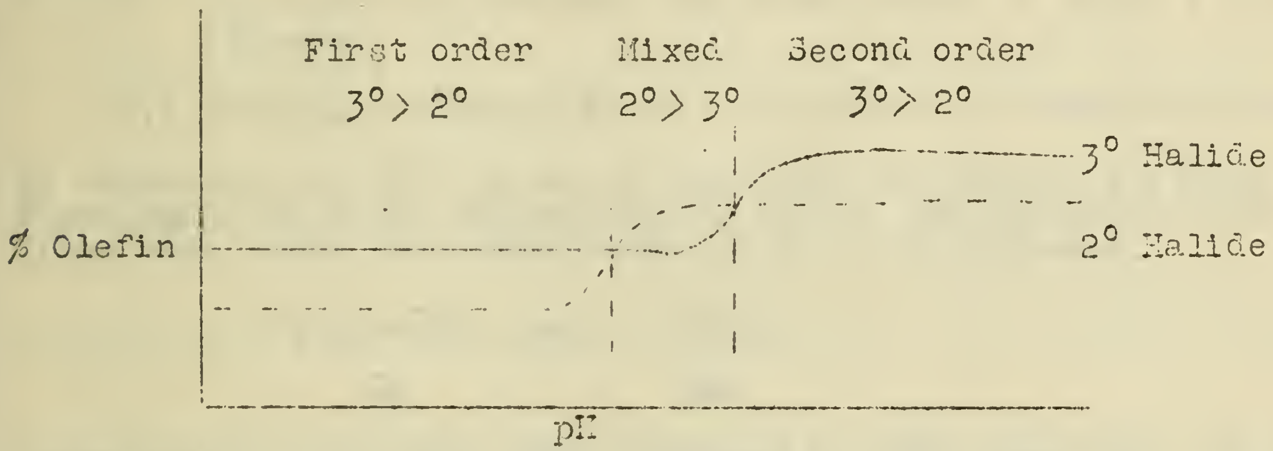
(1) [illegible] — [illegible]

[illegible]

[illegible]

An interesting illustration of the importance of [illegible]

Empirically it has been found that the preparation of olefin which is formed is higher in the bimolecular reaction than in the first order reaction. Consequently, a plot of percent of olefin against pH shows an "S"-like curve, the center portion of which represents the transition from second order to first order kinetics. It will be shown later that an additional R group in the tertiary group increases the proportion of olefin formed in both the first and second order reactions, but we have already seen that carbonium ion formation is favored by the introduction of alkyl groups and particularly methyl. Consequently, more reagent will have to be added to the tertiary halide than to the secondary halide to convert the mechanism from first order to second order. This situation can be represented as follows:



From these curves it can be seen that in order to compare the percent of olefin formed from different halides it must be first determined that the reactions are proceeding by a homogeneous mechanism. In the intermediate cases the normal order may be reversed.

2.) Ionizing Power of the Medium.--In the following table is summarized the distribution of charge in the transition state of the different mechanisms and the effect an increase in the ionizing power of a solvent would have upon ease of formation.

Effect of a More Ionizing Solvent on E and S

Classification	Trans. State	Effect on Charge	Effect on Reactivity
Sn$_2$	$Y^- + RX \rightarrow \overset{-\delta}{Y}\text{-R-}\overset{-\delta}{X}$	Dispersed	Decreased
E$_2$	$Y^- + RX \rightarrow \overset{-\delta}{Y}\text{-H-C-C-}\overset{-\delta}{X}$	Greatly dispersed	Decreased
Sn$_1$ or E$_1$	$RX \rightarrow \overset{+\delta}{R}\text{—}\overset{-\delta}{X}$	Increased	Large increase

Sn_2	$Y^{\ominus} + \overset{\oplus}{R}X \rightarrow \overset{-\delta}{Y}\text{-}R\text{-}\overset{+\delta}{X}$	Reduced	Large decrease
E_2	$Y^{\ominus} + \overset{\oplus}{R}X \quad \overset{-\delta}{Y}\cdots\text{-}H\text{-}C\text{-}C\text{-}\overset{+\delta}{X}$	Reduced	Large decrease
Sn_1 or E_1	$\overset{\oplus}{R}X \rightarrow \overset{+\delta}{R}\text{—}\overset{+\delta}{X}$	Dispersed	Decreased

The conclusions reached in the last column are based upon the following assumptions:

1.) Solvation facilitates the development of point charges (dipoles)

2.) Solvation hinders their dissipation of neutralization.

In comparing Sn_2 with E_2 it is important to observe that the charge dissipation in E_2 is larger than E_1 since the transition state provides more atoms over which the charge is distributed.

Y-H-C-C-X vs.	Y-C-X
E_2	Sn_2

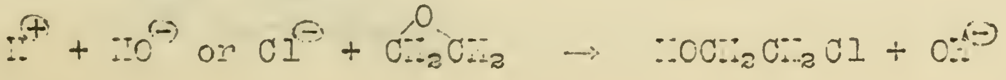
Consequently, ionizing media suppress E_2 more than Sn_2. It is therefore clear why dry, alcoholic potassium hydroxide is a good reagent for the preparation of olefins from alkyl halides.

3.) Basicity of the Reagent.--It is readily seen that the driving force of the second order reactions is the nucleophilic power of the reagent. Experience has shown that it generally increases in the order

$$Br^{\ominus} < OAc^{\ominus} < O\phi^{\ominus} < OH^{\ominus} < OR'^{\ominus}$$

The main effect, therefore, of increasing the basic strength is to increase the second order reaction at the expense of the first order reaction.

In comparing Sn_2 with E_2 we have to evaluate the relative nucleophilic activity of the reagent towards H and C. The parallelism is by no means exact and the general direction of the deviation is that while strong bases are strong towards H, weak bases undergo displacements on C more readily than their basicity would indicate they should. The extreme ease with which halides undergo exchange reactions with the corresponding ions and the fact that an aqueous solution containing potassium chloride and ethylene oxide rapidly becomes basic may be cited as examples of this behavior.



$$H^{\oplus} + HO^{\ominus} \text{ or } Cl^{\ominus} + \overset{O}{CH_2CH_2} \rightarrow HOCH_2CH_2Cl + OH^{\ominus}$$

Clearly therefore as we pass from OR' to Br^- we must observe a decrease in E_2. Such a decrease in the tendency of a given compound to form olefins when treated with a weaker base is well known. It is the reason why alcohols are often prepared from alkyl halides by treating them with potassium acetate and then saponifying rather than by allowing them to react with alkali directly.

4.) Structural Effects.--By far the most important consideration of the course a reaction will take is the structure of the compound within which elimination is to occur. Two important rules concerning elimination have been developed empirically, and it should be interesting to see if they can be incorporated in a more general scheme.

> Hofmann Rule: In the decomposition of quaternary hydroxides that olefin will be formed which has the smallest number of alkyl groups attached to it.
>
> Saytzeff Rule: When a halide is converted to an olefin, the most highly branched olefin will be formed.

In a careful study of elimination reactions designed to determine whether the differences of the Hofmann and Saytzeff rules might be due to

1.) Nature of the alkyl compound (halide or 'onium)
2.) Type of alkyl group (i.e., 1°, 2°, or 3°)
3.) Mechanism of the reaction

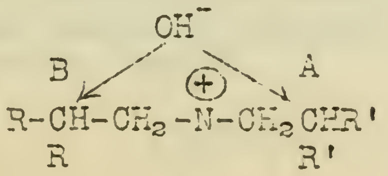
The following results were obtained:

Control of the H. or S. Rule in Elimination Reactions

Mech.	'onium Ions			Halides		
	1°	2°	3°	1°	2°	3°
E_2	H	H	H	S	S	S
E_1		S	S		S	S

Clearly the problem is a complex one since different rules are followed in the E_2 reaction yet both are presumed to occur by the same mechanism.

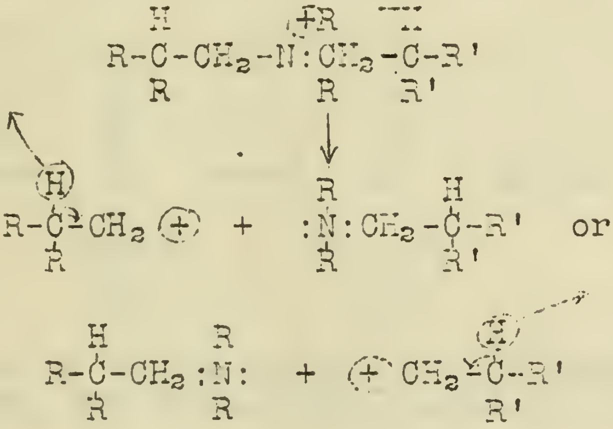
An examination of the possibilities for combination of a hydroxyl ion with a hydrogen atom in an 'onium compound reveals that in the E_2 reaction attack should occur at the hydrogen atom of lowest electrical density.



Since alkyl groups exhibit electron release by I_D, attack will occur either at the β carbon atom having the fewest alkyl groups attached to it or, if there are R groups attached to both B carbon atoms, displacement should occur at the one holding the group of poorest electron release. The order of I_D is

$$(CH_3)_3C- > (CH_3)_2CH- > RCH_2- > CH_3CH_2- > CH_3-$$

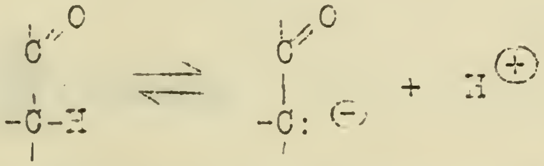
On the other hand in the first order mechanisms a proton should be eliminated from the most highly substituted β carbon atom in accordance with Saytzeff's rule.



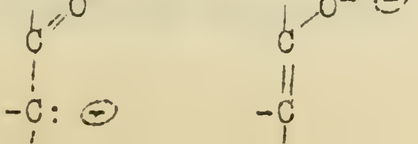
Of the two possibilities shown, that one will occur which most helps the electronic shift shown by an inductomeric electron release I_D.

In the case of the E_2 reaction of the halides Hofmann rule is reversed. This appears to be another example of what has come to be recognized as the Hyperconjugation Effect of Alkyl Groups.

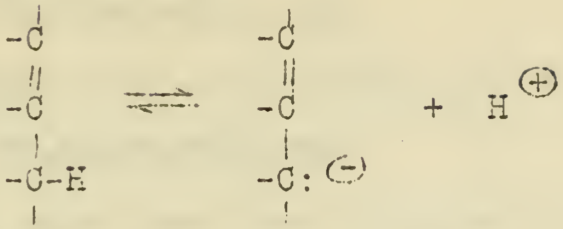
This effect will be discussed in more detail under the topic of "Resonance," but without entering the subject too deeply at this point an idea of its implications may be obtained by an examination of the activating influence of a carbonyl group. It is well known that a hydrogen atom on an α carbon atom has acidic properties. (Acetoacetic ester, for example, is about as strong an acid as phenol). Accordingly we can write the equilibrium



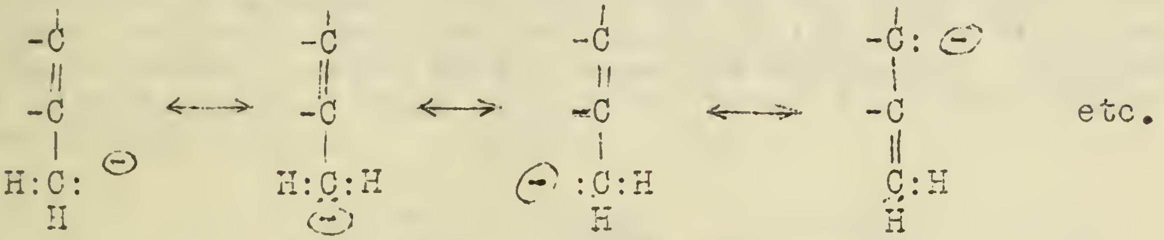
regardless of where the position of equilibrium lies. In the case of the system shown, the equilibrium lies further to the right than would normally be expected because the anion is much more stable than would be expected due to the fact that it can exist as a resonance hybrid.



Similarly, in the equilibrium

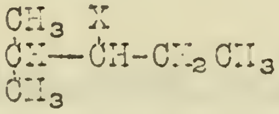


the position of equilibrium lies further to the right than might be expected because the anion in this case is stabilized by the resonance forms.



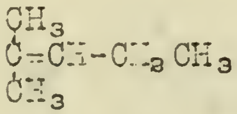
The application of the principle of hyperconjugation to elimination reactions, then, may be stated something like this:

In the absence of a powerful inductive effect within a molecule (e.g., $\overset{\oplus}{N}$, or $\overset{\oplus}{S}$) the position the double bond takes is such that it is conjugated with the greatest possible number of hydrogen atoms on the carbon atoms α to it. Thus in an elimination reaction of the compound



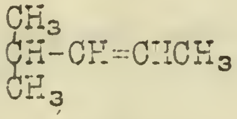
$$\underset{CH_3}{\overset{CH_3}{C}}H-\overset{X}{C}H-CH_2CH_3$$

the olefin which would be produced would be



$$\underset{CH_3}{\overset{CH_3}{C}}=CH-CH_2CH_3$$

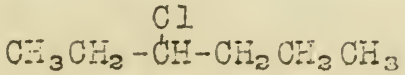
rather than



$$\underset{CH_3}{\overset{CH_3}{C}}H-CH=CHCH_3$$

since in the first case there are 8 hydrogen atoms on the carbon atoms α to a double bond while in the second there are only 4.

Similarly, more of a mixture would be expected in the case of



$$CH_3CH_2-\overset{Cl}{C}H-CH_2CH_2CH_3$$

since

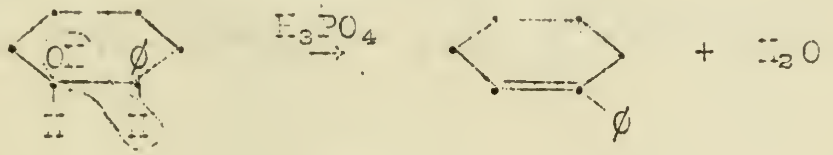
$$CH_3CH{=}CH{-}CH_2CH_2CH_3$$

has 5 hydrogen atoms on α carbon atoms whereas

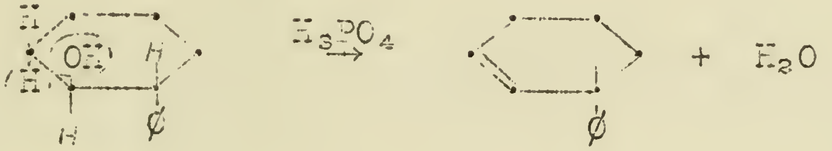
$$CH_3CH_2CH{=}CHCH_2CH_3$$

has 4. Many such cases have been examined and the principle appears to be quite general.

Stereochemistry of Elimination Reactions: In the case of the dehydration of alcohols which proceed by E_1 mechanisms, there again is clear evidence that the carbonium ion (if it be an intermediate in the reaction) cannot have a separate existence. Elimination, like displacement, always appears to involve elements which are trans to each other.

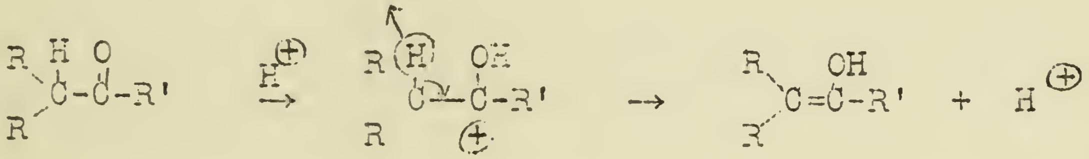

OH
ø
H
H
H_3PO_4
ø
+ H_2O

but


H
OH
H
H
H
ø
H_3PO_4
ø
+ H_2O

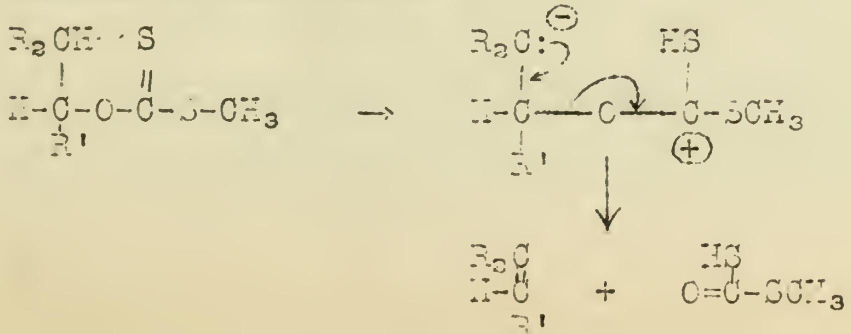
Other Reactions Which Appear to Proceed by Elimination:

1.) Acid-Catalyzed Enolization.

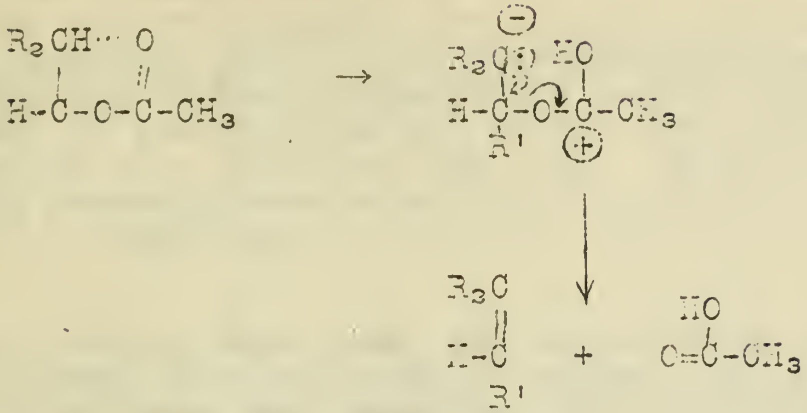

R
H
O
C-C-R'
R
$H^{\oplus}$
R
(H)
OH
C-C-R'
R
⊕
R
OH
C=C-R'
R
+ H⊕

(To be discussed under "Acid-Catalyzed Condensation Reactions")

2.) Tschugaeff Reaction.


R_2CH
S
H-C-O-C-S-CH$_3$
R'
$R_2C:$ ⊖
HS
H-C—C—C-SCH$_3$
R'
⊕
R_2C
H-C
R'
+
HS
O=C-SCH$_3$

3.) Acetate Decomposition.


R_2CH
O
H-C-O-C-CH_3
⊖
R_2C
HO
H-C-O-C-CH_3
R'
⊕
R_2C
H-C
R'
+
HO
C=C-CH_3

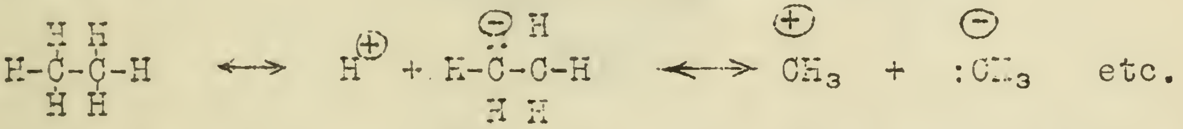
Bibliography

Hughes and Ingold, Trans. Farad. Soc., 37, 657-686 (1941).

General.--Insofar as most organic chemists are concerned the the principle of resonance may be stated somewhat as follows:

> If for a given compound two or more structures may be written differing only in the distribution of electrons, the properties of that compound will not be those to be expected of any of the formulas but rather they will be those to be expected of a hybrid of them all. An ion or molecule in which resonance can occur will always be more stable than would be expected.

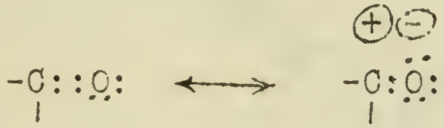
It is obvious that when the principle is stated in such general terms no attempt has been made to explain the phenomenon, but rather the conditions have been described for recognizing its occurrence. Further it is clear that since each covalent bond may have a certain amount of ionic character, resonance forms may actually be written for every organic compound and the problem we are concerned with in discussing resonance is one of deciding which forms will contribute significantly towards making up the hybrid. Thus for ethane the structures



$$H_3C{-}CH_3 \longleftrightarrow \overset{\oplus}{H} + \overset{\ominus}{\ddot{C}}H_2{-}CH_3 \longleftrightarrow \overset{\oplus}{CH_3} + :\overset{\ominus}{CH_3} \quad \text{etc.}$$

I II III

might be written. Except in unusual cases (e.g., ultraviolet absorption spectra) the forms such as II and III contribute so little towards the hybrid that they may be neglected. Similarly, the carbonyl group may be written



$$-\underset{|}{C}::\ddot{O}: \longleftrightarrow -\underset{|}{\overset{\oplus}{C}}:\overset{\ominus}{\ddot{O}}:$$

IV V

but here since dipole moment studies indicate a large contribution of the form V, (47%), resonance is important and the deviations of the properties of the carbonyl group from those to be expected of form IV will be large.

In more complex cases a certain amount of intuition is required in order to judge whether a resonance form contributes much or little to the structure of a compound. The following rules are often helpful.

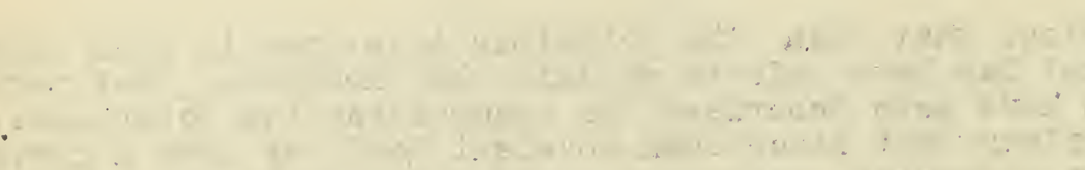
The Conditions for Important Resonance Contributions.

1) Resonance can occur only between structures that correspond to the same or to very nearly the same relative positions of all

[illegible]

> [illegible]

[illegible]



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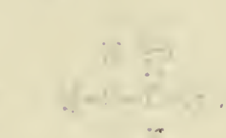


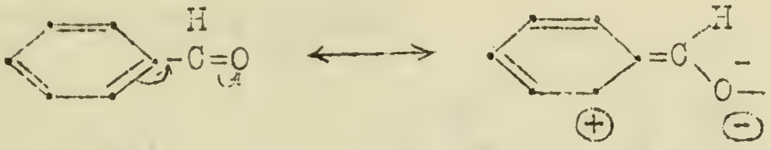
[illegible]

[illegible]

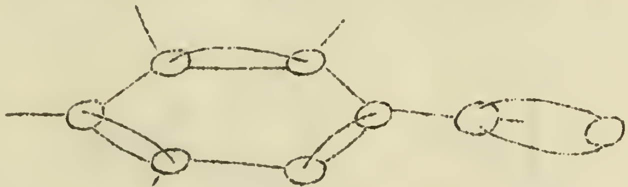
[illegible]

1) [illegible]

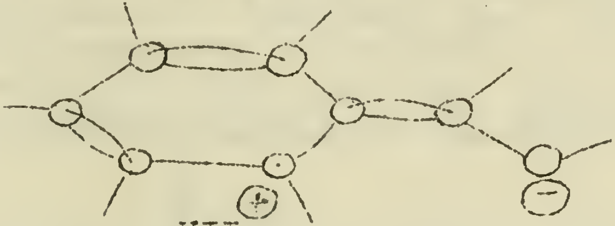
the atomic nuclei. It is this requirement which rules out tautomerism as a form of resonance (a hydrogen atom shifts) and imposes the condition of coplanarity of the atoms of a resonating system. This can most easily be seen in the case of functional groups which enter into resonance with a benzene ring. Consider, for example, the resonance forms VI and VII.


VI VII

Examination of models shows that in VI while the C, H and O atoms may be in a plan perpendicular to the plane of the benzene ring (VIa),


(VIa)

the shift of a double bond from the ring to the carbon atom of the aldehyde group as in VII requires that the C, H, and O atoms all must fall in the same plane as the benzene ring if the tetrahydral configuration of a carbon atom is to be maintained (VIIa).


VIIa

Resonance, therefore, can occur only when all of the atoms involved lie in the same plane.

2) The energy of the structures should be approximately the same as estimated by the use of the so-called bond energies.

3) With atoms arranged in a ring, only those valence bond structures for which the bonds do not cross need to be considered.

4) Unperturbed structures in which adjacent atoms have electrical charges of the same sign are much less important than other structures.

5) Other things being equal the most stable form will have the greatest number of covalent bonds and formal plus or minus charges residing on the most electropositive or electronegative atoms, respectively.

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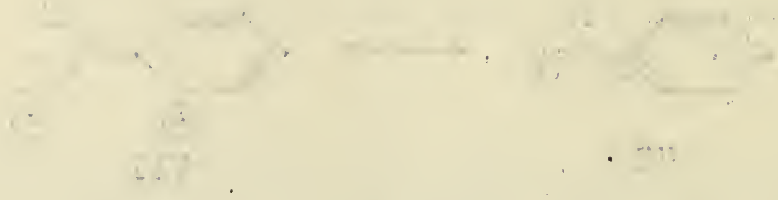


[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

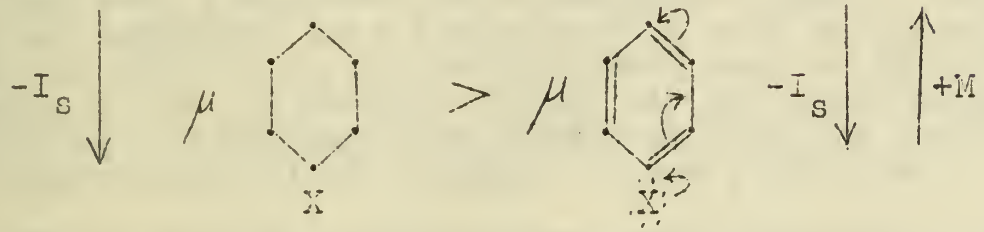
Manifestations of Resonance:

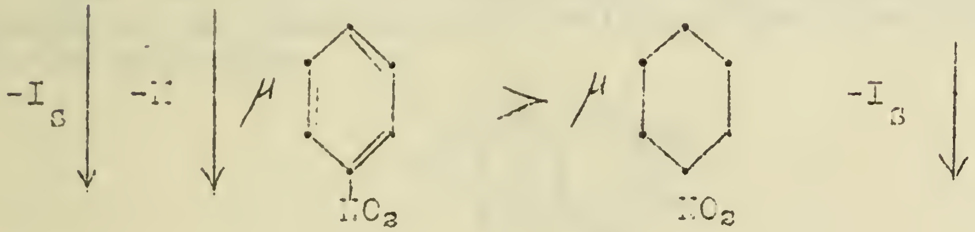
1) Heats of hydrogenation are lower than would be predicted.

2) Heats of combustion are lower than would be predicted.

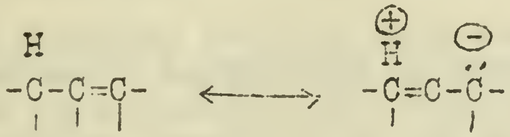
3) Bond distances are shortened.

4) Dipole moments are affected.





Hyperconjugation.--In the discussion of elimination reactions attention was called to the fact that the carbon-hydrogen bond at a position α to a double bond is somewhat weaker than would be expected. This must mean that electrons are withdrawn from this bond or conversely that a carbon-hydrogen bond so situated is capable of electron release by some mechanism other than I_s. This particular kind of resonance is called Hyperconjugation or No Bond Resonance. It may be represented as



$$\overset{H}{-C}-C=C- \longleftrightarrow \overset{\overset{\oplus}{H}}{-C}=C-\overset{\ominus}{\ddot{C}}-$$

in which the form shown on the right makes a small - but sometimes noticable - contribution to the resting state of the molecule. In addition to its effect in elimination reactions, there is other evidence for the existence of hyperconjugation.

1) The heats of hydrogenation of propylene and ethylene differ about as much and in the same direction as 1,4-pentadiene and 1,3-butadiene.

2) Bond distances are shortened when hyperconjugation can operate.

3) The S_{N_1} hydrolysis of p-alkylbenzhydryl chlorides is in the order

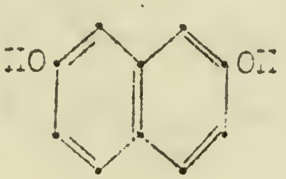
$$H < \left[CH_3 > Et > \underline{iso}\text{-}Pr > \underline{t}\text{-}Bu\right]$$

4) The Sn_2 reaction of *p*-alkylbenzyl chlorides with pyridine is in the same order.

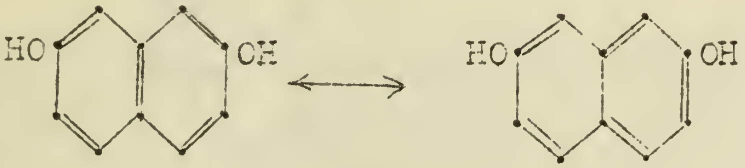
5) The combined *o,p*-bromination of toluene proceeds four times faster than that of *t*-butylbenzene showing that a methyl group exhibits greater electron release than a *t*-butyl group when it is connected to a conjugated system.

Bond Fixation.--The principle of bond fixation (Mills-Nixon Effect) has long been associated with resonance theory. Although recent work has suggested that the effect is much smaller than was originally thought, it is interesting that some of the evidence taken as support of the Mills-Nixon Effect may be interpreted in such a way that it is not necessary to postulate that the bonds in the unreacting molecule are fixed rigidly in one structure.

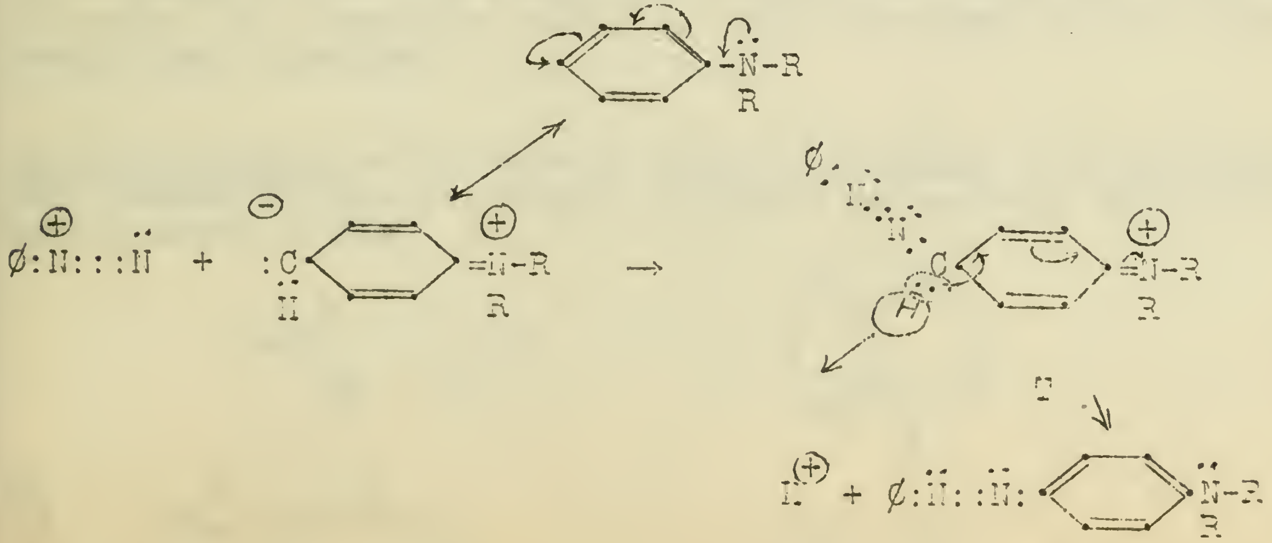
The fact that 2,7-dihydroxy naphthalene couples only in the 1 or 8 position has been taken as evidence that the dihydroxy naphthalene has the structure



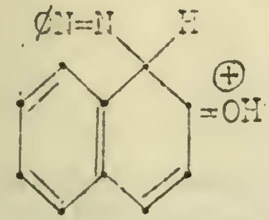
rather than the hybridized resonance form



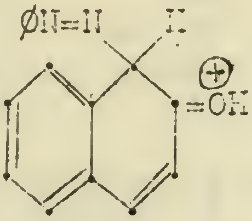
In diazonium coupling it will be observed that a free electron pair on an atom adjacent to the ring appears to be necessary for the aromatic ring to be coupled with a diazonium cation. Since the cation carries a positive charge it is to be expected that reaction will occur as a result of electron release (E) from the unshared pair so as to create a surplus of electrons in the ortho or para positions.



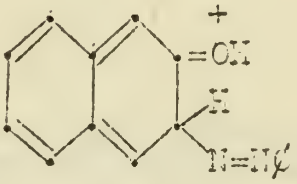
Regardless, therefore, of where the double bonds are in the resting state it is the electronic distribution in the transition state T which will determine the position of coupling. Applying this reasoning to the case of 2,7-dihydroxynaphthalene it is apparent that the two structures possible for coupling in the 1 or 8 position should be the more stable since they retain the full resonance energy of an intact benzene ring while the transition state complex for coupling in the 3 position does not.



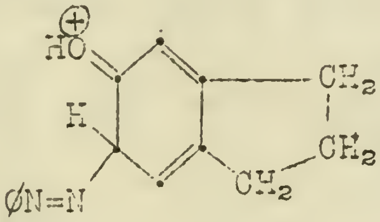
or



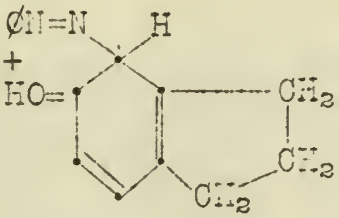
vs.



Similarly in the case of 5-hydroxyhydrindene the transition state complex



should be more stable than

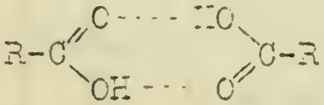


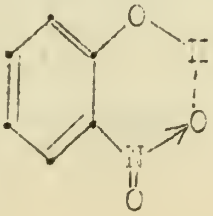
since the C_8-C_9 bond is stretched by a spring-like action of the five-membered ring so that its length is nearer to the single bond value.

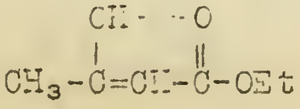
Clearly these considerations are simply another way of looking at the same problem, but they get around the seemingly valid objection that the resonance energy of these compounds is too high to permit bond fixation.

--

Hydrogen Bonding.--The type of chemical bonding in which a hydrogen atom serves to hold two others together is known as hydrogen bonding. Common examples are






$$\overset{\text{CH}\cdots\cdots\text{O}}{CH_3\text{-}C\text{=}CH\text{-}C\text{-}OEt}$$

H-F...H-F

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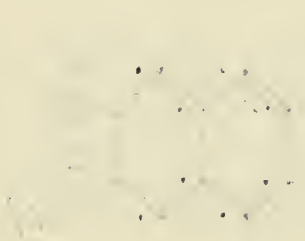

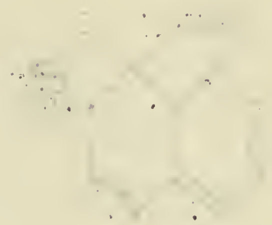

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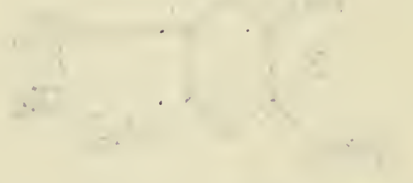

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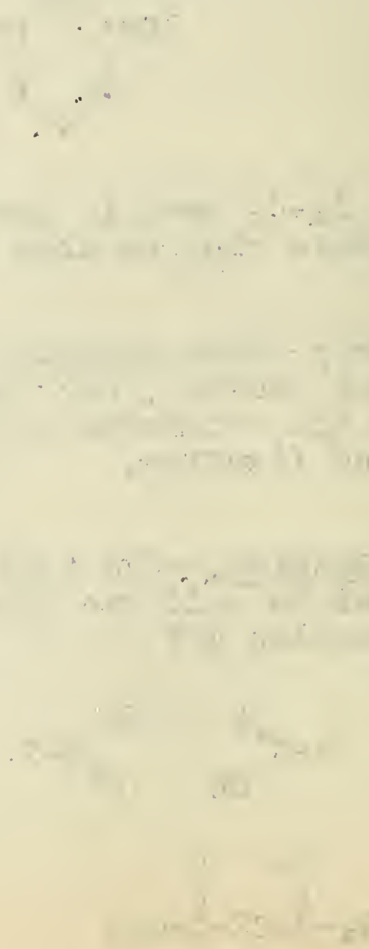
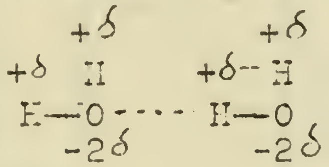
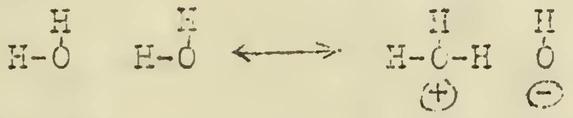


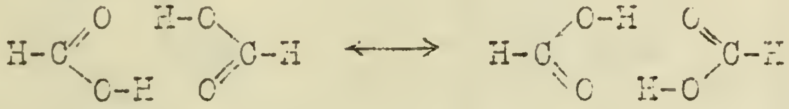
As yet there is no general agreement with regard to the nature of the forces responsible for the hydrogen bond. Quantum mechanics has shown that a hydrogen atom with four electrons in its valence shell would be very unstable. Alternatively hydrogen bonding may be interpreted as an electrostatic or a resonance phenomenon. From the point of view of an electrostatic phenomenon hydrogen bonding occurs as a result of the partial ionic character of the H-O or H-N bonds. In the case of water the situation may be shown as follows:



Thus while each of the molecules is neutral as a whole the two are attracted together. The failure of, say, acetone to behave similarly may be due to steric hindrance.

The interpretation of hydrogen bonding as a resonance phenomenon and the objections to it may be shown with formic acid and water.



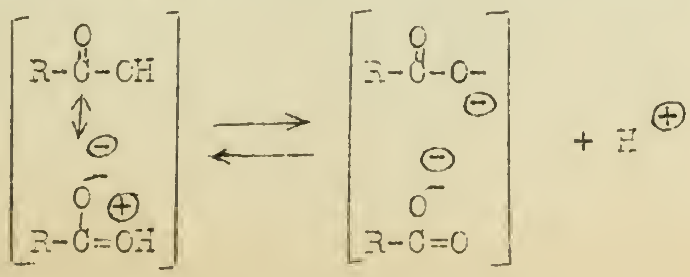


It will be observed that in the charged form for water the two structures are not equivalent while the two shown for formic acid are. Experience has shown that stabilization due to resonance is tremendiously greater when the structures are equivalent and of the same stability. Dimeric formic acid, therefore, should have a much greater energy of dissociation than water. Actually it is only about 50% greater than water. Further evidence that the hydrogen atom is not at the center of the bond has been obtained from electron difraction and spectroscopic studies which indicate that an O-H---O bond is considerably more than twice the ordinary O-H distance. If the hydrogen atom is in the center, the O-H bond in each structure must have been greatly stretched.

Examples of the Effects of Resonance:

1) Strength of Acids.--A partial explanation of the cause of acidity and basicity is to be found in the fact that in many cases after gaining or losing proton there are great possibilities for resonance.

a)



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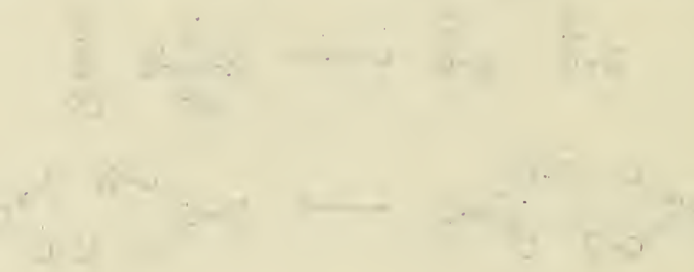

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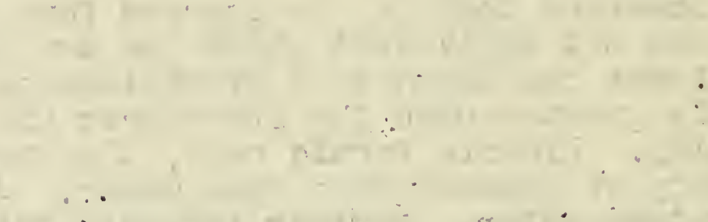

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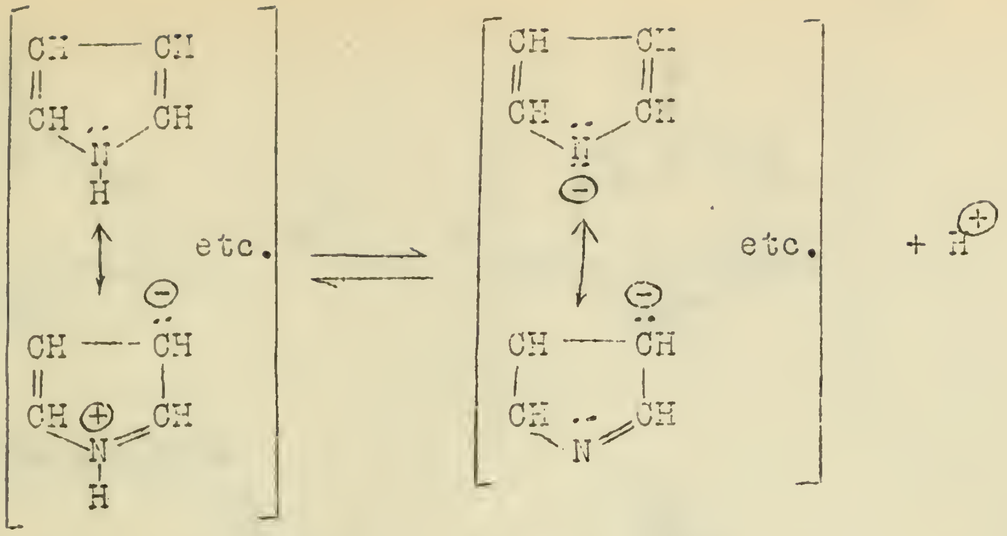
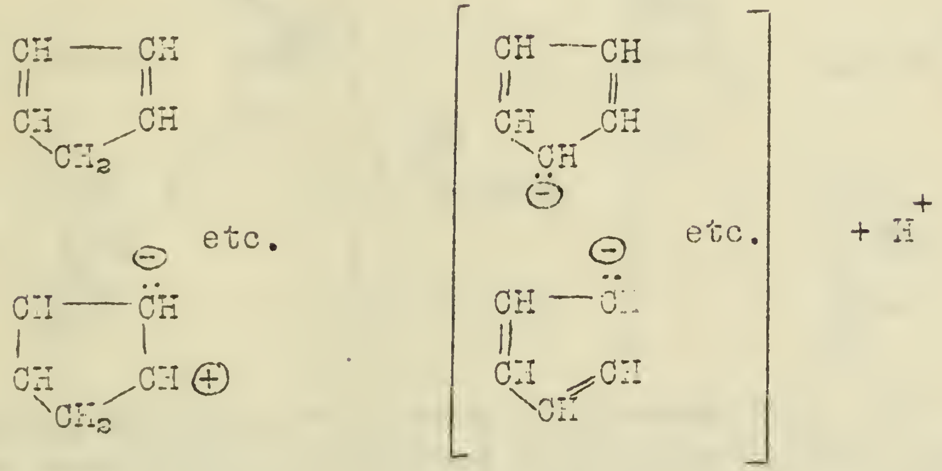
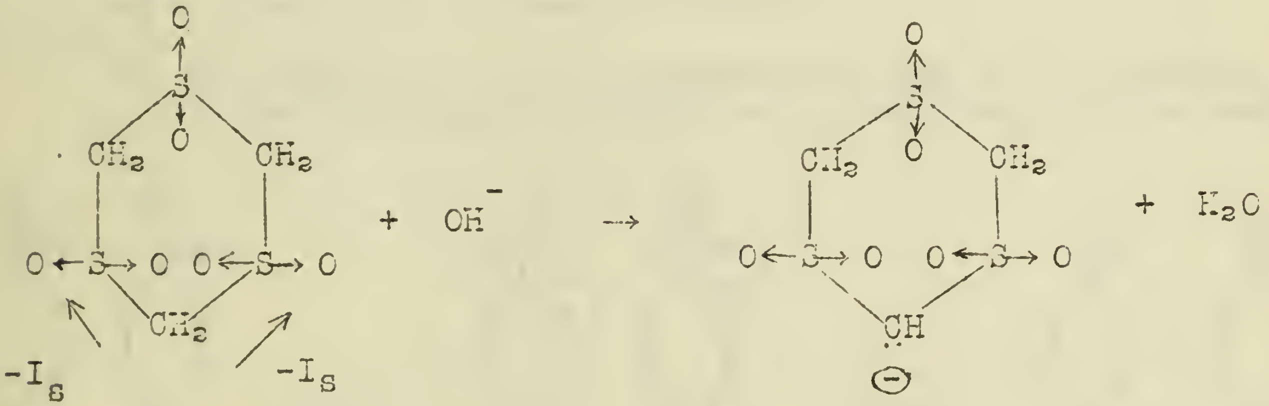
b)



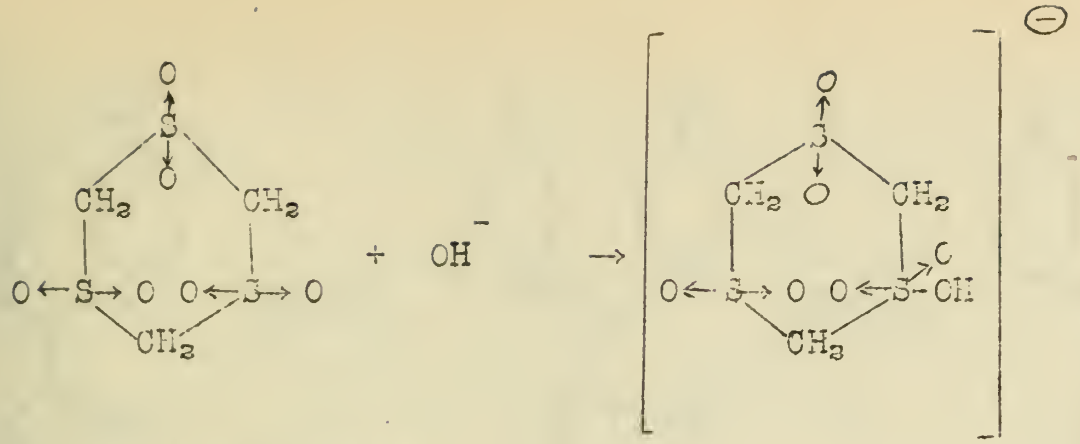
c)



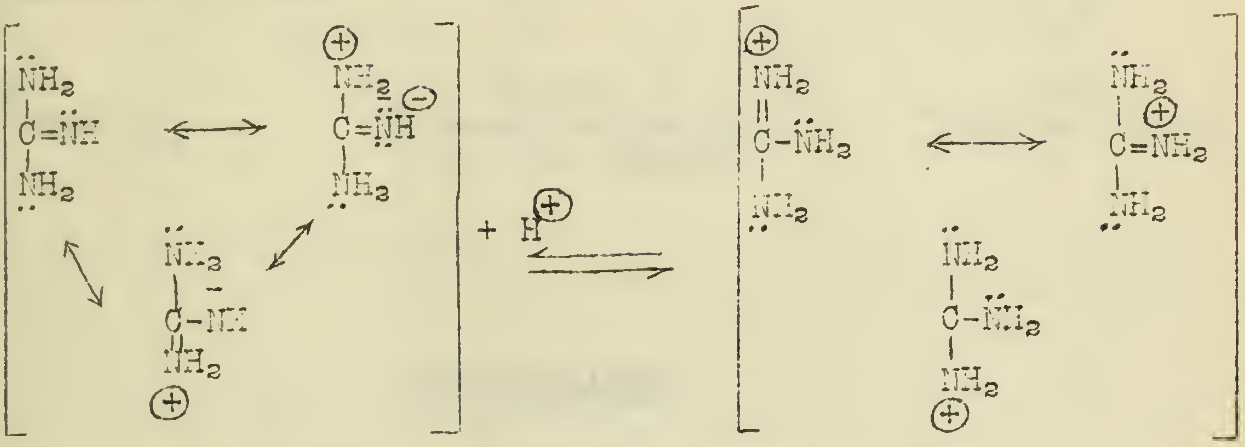
Although resonance is an important factor in ionization it is not a necessary one. Trimethylene sulfone and trimethylene sulfoxide dissolve in dilute alkali. This may be interpreted as due entirely to inductive effect



or to the ability of S to increase its valence shell to 10.



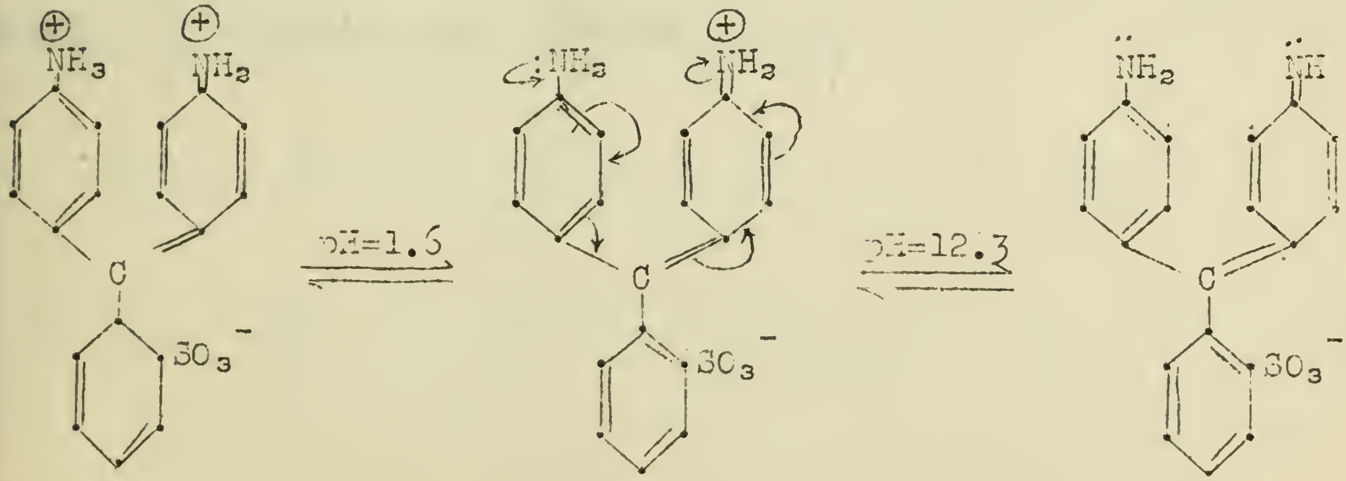
2) Strength of Bases



3) Production of Color.--In terms of present day color theory intense absorption is observed when approximately equivalent resonance forms may be written such that the change from one to the other involves the movement of a unit electronic charge. It is important to observe that absorption will be less intense if

a) a formal charge does not shift.

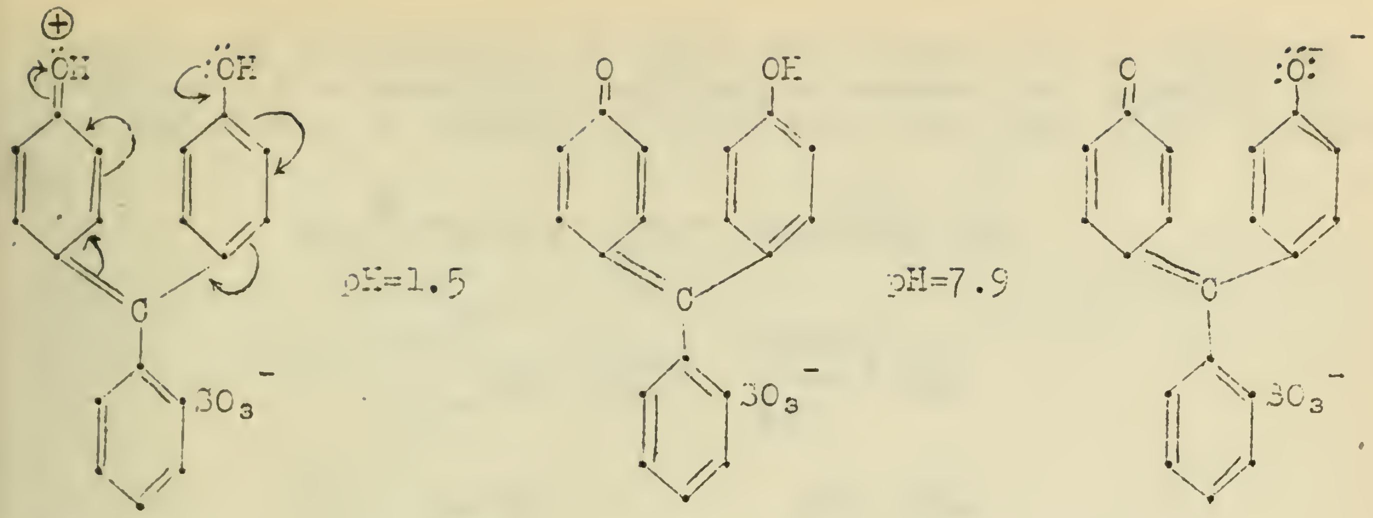
b) the capacity of the auxochrome to act as an electron source or the chromophore to act as an electron sink is destroyed.



Yellow (auxochrome destroyed)

Violet (Charge Shifts)

Yellow (Resonance involves *no* unit charge)



Red
(charge shifts)

Yellow
(Resonance involves
no unit charge)

Red
(charge shifts)

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General: 1) Wheland, "The Theory of Resonance"
2) Remick, "Electronic Interpretation of Organic Chemistry", pp. 133-187

Bond Fixation: Wheland, pp. 269-272

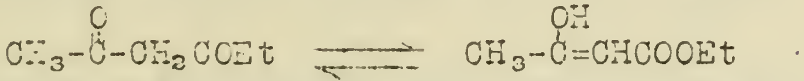
Hydrogen Bonding: Wheland, pp. 44-51

Acid and Base Strength:

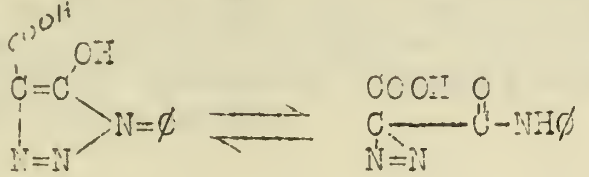
1) Wheland, pp. 167-190
2) Remick, pp. 146-152

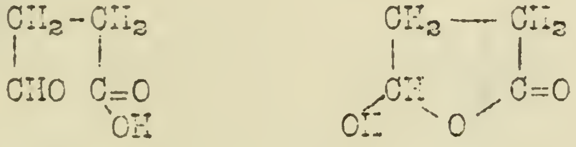
Color: Remick, pp. 173-186

General.--By tautomerism, as Baker has defined it, is meant the occurrence of a reversible equilibrium between two isomers. In this definition is included such diverse reactions as the following:

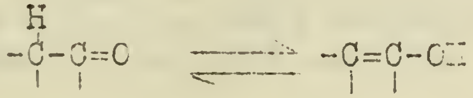


$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2COEt \rightleftharpoons CH_3-\overset{OH}{\overset{|}{C}}=CHCOOEt$$





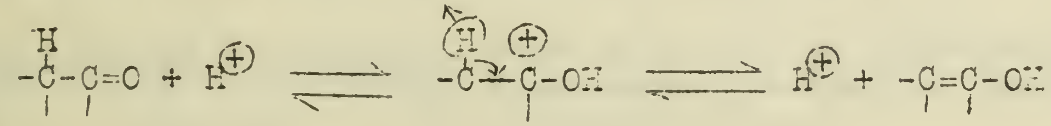
For the purposes of this discussion, however, it would be better to restrict the term to the reversible interconversion of keto and enol forms.



$$-\overset{H}{\underset{|}{C}}-\underset{|}{C}=O \rightleftharpoons -\underset{|}{C}=\underset{|}{C}-OH$$

Mechanism of Tautomerism.--It is an important fact to remember in discussing the mechanism of tautomerism that when the apparatus for distillation is scrupulously freed of all traces of acids or bases, certain compounds have been separated into a keto and an enol form. This, of course, does not rule out the possibility that a slow intramolecular transformation may occur, but it is quite clear that a much more rapid equilibration requires the presence of acid or base.

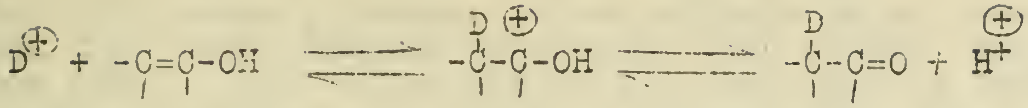
Acid-Induced Enolization.--The acid-induced enolization is assumed to proceed by the addition of an acid to the oxygen of the carbonyl group which initiates an elimination-like reaction and which results in the loss of a proton from an α carbon atom.



$$-\overset{H}{\underset{|}{C}}-\underset{|}{C}=O + H^{\oplus} \rightleftharpoons -\overset{(H)}{C}-\overset{\oplus}{\underset{|}{C}}-OH \longrightarrow H^{\oplus} + -\underset{|}{C}=\underset{|}{C}-OH$$

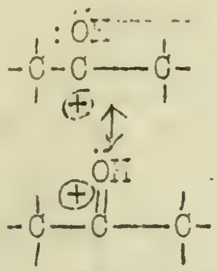
It is clear that when a proton is the acid which is used, it is not the same hydrogen atom attached to the α carbon atom which becomes attached to the oxygen atom and conversely the transformation from an enol to a keto form does not involve the same hydrogen atom. It is a well-known fact that hydrogen atoms on a carbon atom α to a carbonyl group can be replaced by deuterium in the presence of deuterium oxide. Presumably the reaction may be written

$$H^{\oplus} + D_2O \rightleftharpoons D^{\oplus} + DOH$$

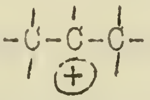


$$D^{\oplus} + -C{=}C{-}OH \rightleftharpoons -\overset{D}{C}{-}C{-}OH^{\oplus} \rightleftharpoons -\overset{D}{C}{-}C{=}O + H^{+}$$

In comparing acid-induced enolization with E_1 it is evident that the two systems are quite similar differing only in the fact that the intermediate I should be somewhat more stable than II due to added resonance forms shown.

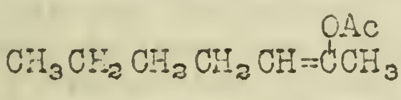


I



II

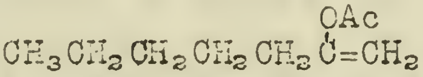
The position of the double bond, therefore, should be that which allows the maximum number of hyperconjugation forms. As an example consider the formation of an enol acetate from methyl n-amyl ketone. There are two possibilities, III and IV.



$$CH_3CH_2CH_2CH_2CH{=}\overset{OAc}{C}CH_3$$

III

or



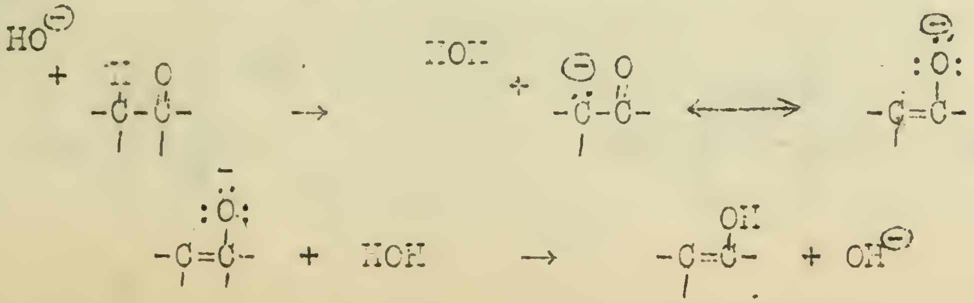
$$CH_3CH_2CH_2CH_2CH_2\overset{OAc}{C}{=}CH_2$$

IV

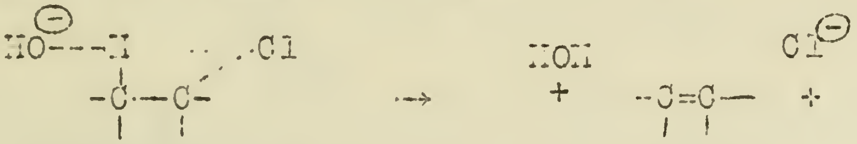
In form III there are 5 hydrogen atoms α to the double bond whereas in form IV there are 2. It has been shown that the enol acetate prepared from the ketone and acetic anhydride in the presence of p-toluene sulfonic acid is 100% form III.

As will be discussed later, it is assumed that it is the position of the double bond which determines the products obtained in halogenation and condensation reactions.

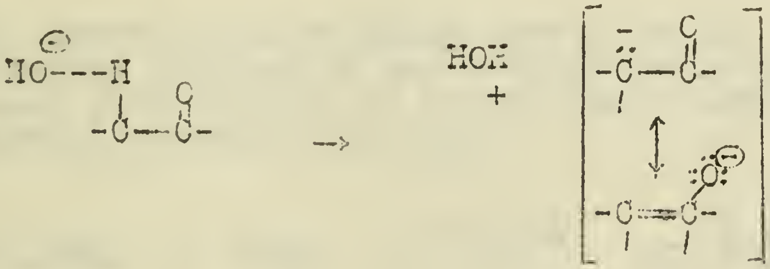
Base-Induced Enolization.--The mechanism of base-induced enolization differs from acid-induced enolization in that it involves a nucleophilic displacement on an α hydrogen atom.



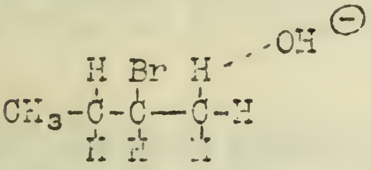
Here again will be observed the similarity of this reaction to elimination reactions, this time of the E_2 type. There is one important difference, however, which appears to be responsible for the fact that basic-induced reactions occur at the least substituted α carbon atom. That difference is the fact that in the formation of the reactive enolate ion no bond is broken after the transition state is reached which can exert an attraction for electrons. Thus the decomposition of the transition state complex in the case of E_2 reactions may be written



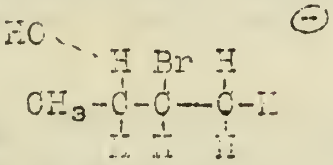
while in the case of base-induced enolate formation it may be written



At the time elimination reactions were discussed, the exact mechanism by which hyperconjugation affects the location of the double bond was not considered. The influence it exerts, however, is actually believed to affect bond breaking -- i.e., the decomposition of the transition state. Thus in an elimination reaction of secondary butyl bromide both V and VI might be formed, but the decomposition of VI is helped most by hyperconjugation.

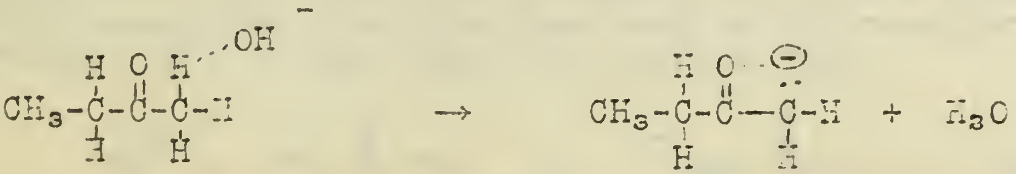


V



VI

Since hyperconjugation does not operate in the formation of the ion, displacement occurs at the hydrogen atom of lowest electron density which is one attached to the α carbon atom of least substitution. A Claisen-Schmidt condensation of benzaldehyde and methyl ethyl ketone therefore produces substitution on the methyl group.



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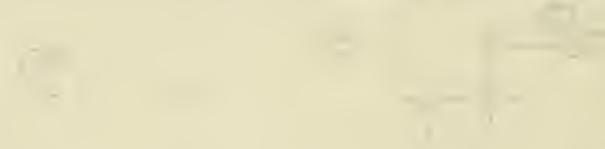

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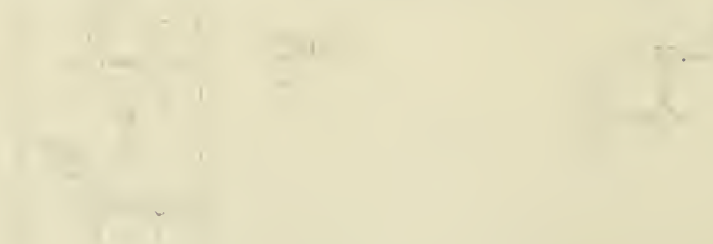

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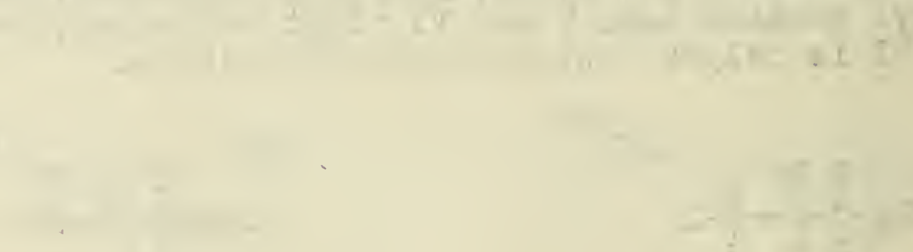

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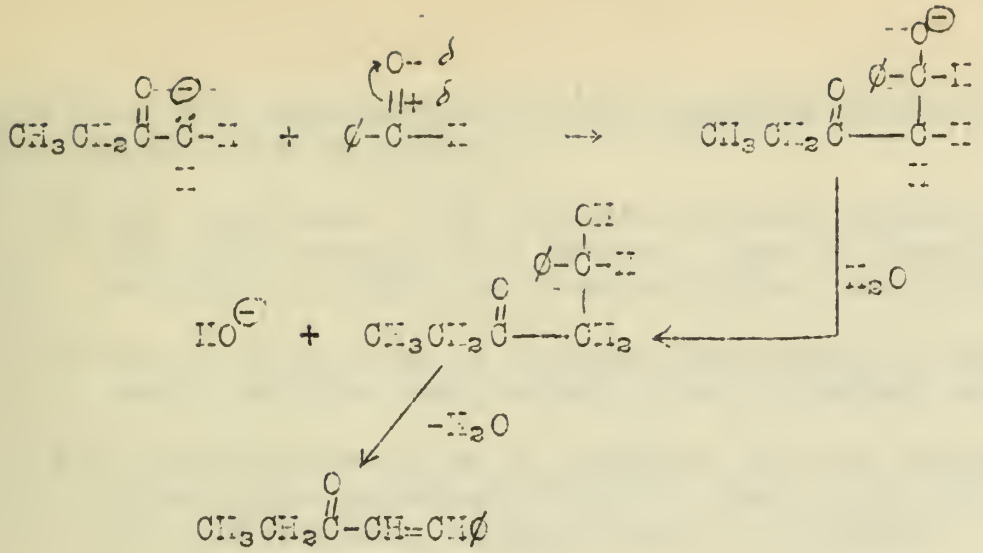
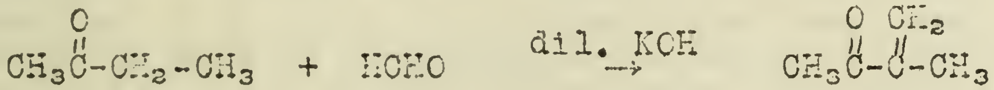


Apparently, however, these factors cannot be the only ones governing the condensation because it has been recently shown that in a crossed aldol condensation of formaldehyde with methyl ethyl ketone methyl propenyl ketone is produced



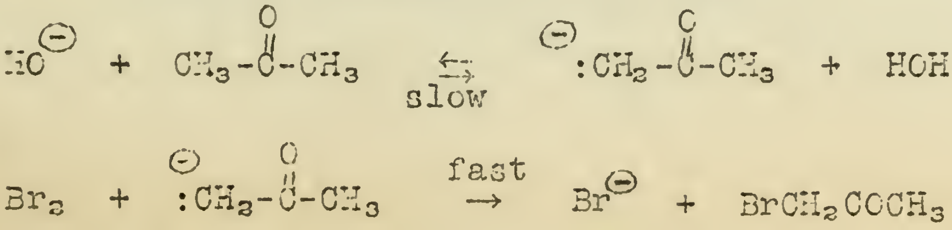
$$CH_3\overset{O}{\overset{\|}{C}}-CH_2-CH_3 + HCHO \xrightarrow{dil.\ KOH} CH_3\overset{O}{\overset{\|}{C}}-\overset{CH_2}{\overset{\|}{C}}-CH_3$$

It is quite important to observe that in terms of present theory it is not necessary to consider that reactionsof this kind involve the transformation of a "keto" to an "enol" form. Rather the necessary and sufficient condition for these reactions is the formation of the carbanion resonance hybrid. "There is no reason to suppose that the formation of an electrically neutral enol form represents anything more than an unimportant bypath into which a portion of the reacting substance may transiently stray." (Hammett)

Base-Induced Ketone Halogenations.--The way in which acids and bases affect the rate of reaction often points toward the reaction mechanism. For example, in the base-induced bromination of acetone, the rate is

1) Proportional to the concentration of acetone.
2) Independent of the concentration of bromine.
3) Proportional to the concentration of base present (although it does not appear in the stoichiometric equation).

Information of this sort can be reconciled with a mechanism based upon the assumption that the slow step in the reaction is the abstraction of a proton from the α carbon atom.



$$HO^{\ominus} + CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \underset{slow}{\rightleftarrows} {}^{\ominus}:CH_2-\overset{O}{\overset{\|}{C}}-CH_3 + HOH$$

$$Br_2 + {}^{\ominus}:CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{fast} Br^{\ominus} + BrCH_2COCH_3$$

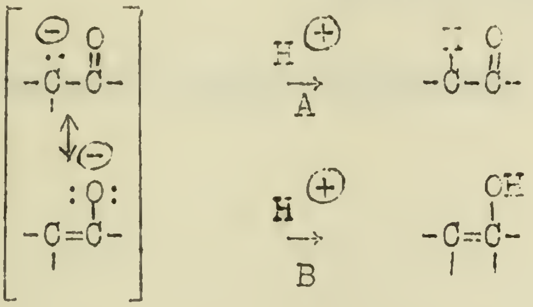
Aside from the mathematics of the reaction there are other facts which support the mechanism.

1) Any substance with proton affinity should be effective for the removal of a proton, more or less according to its basicity. This has been verified quantitatively.

2) In an unsymmetrical ketone halogenation should and does occur at the least substituted α carbon atom.

3) Substitution of an α hydrogen atom by halogen should facilitate the approach of OH^-. The first isolable product in base-induced halogenation is $RCOCBr_3$.

Enolization of Acetoacetic Ester Derivatives.--An interesting point in the theory of the formation of a neutral enol from a keto compound is a comparison of the rate of mutarotation and enol formation of the menthyl ester of α-phenylacetoacetic acid. When the conversion is carried out in hexane solution in the presence of piperidine it is found that mutarotation runs about three times as fast as the rate of formation of the enol. It is necessary, then, to admit the presence of a racemizable intermediate between the keto and enol form. This could be the carbanion but since racemization proceeds faster than enolization, about twice as many ions must revert to the equimolar mixture of d and l ketone as go on to enol. That is the rate of A must be twice that of B.



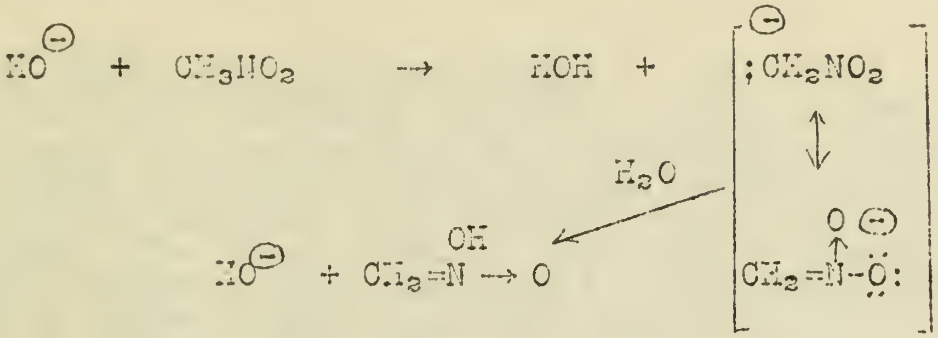
Although it is extremely dangerous to reason about the reactivity of the various forms of a resonance hybrid, the upper form would indeed be expected to be the more reactive (lowest stability). The important point, however, is that even in this case the transformation cannot be written simply

$$\text{Keto} \rightleftharpoons \text{enol}$$

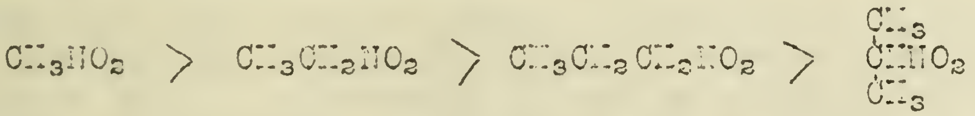
but rather it must involve an intermediate.

$$\text{Keto} \rightleftharpoons \text{intermediate} \rightleftharpoons \text{enol}$$

Base-Induced Enolization of Nitroparaffins.--The transformation of a nitroparaffin into its aci form is another example of a nucleophilic displacement on hydrogen.


$HO^{\ominus}$ + CH_3NO_2 → HOH +
$:CH_2NO_2^{\ominus}$
H_2O
$HO^{\ominus}$ + $CH_2=N(OH)\rightarrow O$
$CH_2=N(\rightarrow O)-\ddot{O}:^{\ominus}$

It is of particular interest because the rate of neutralization of the various nitroparaffins is in the order



$$CH_3NO_2 > CH_3CH_2NO_2 > CH_3CH_2CH_2NO_2 > \overset{CH_3}{\underset{CH_3}{CHNO_2}}$$

while the equilibrium constants vary in the reverse order. This is one of the classical examples of the failure of the usual rate-equilibrium parallelism.

Bibliography

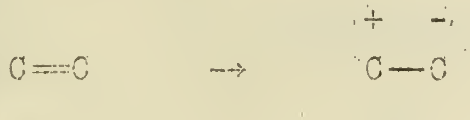
Hammett, "Physical Organic Chemistry," pp. 96-99, 104-111, 229-250.

The present discussion of additions to carbon-carbon double bonds will be concerned with reactions which appear to follow ionic or polar mechanisms. Free radical reactions involving carbon-carbon double bonds will not be considered.

Nature of the Carbon-Carbon Double Bond.

The double bond connecting two carbon atoms differs appreciably from a single bond connecting two carbon atoms. This difference is reflected in greater electron polarizability and in the high energy barrier against free rotation which gives rise to *cis-trans* isomerism. The double bond is believed to consist of one ordinary type linkage of two electrons (electrons) and, in addition, a bond of lower energy containing the so-called π electrons. This pair of electrons is less firmly held between the two nuclei and is responsible for the high polarizability and chemical reactivity of unsaturated compounds.

Although some authors [Price, Reactions at Carbon-Carbon Double Bonds] discuss the various reactions of carbon-carbon double bonds in terms of the π electrons, it may be simpler for the present discussion, to consider reactions of the double bond as proceeding through the intermediate B.



$$C{=}C \longrightarrow \overset{+}{C}{-}\overset{-}{C}$$

A B

The point of attach and the nature of the products obtained will therefore be determined by the direction of the electromeric shift shown.

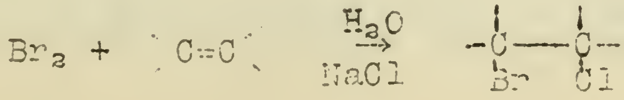
Addition Reactions

A large number of experimental facts have been collected, from which we may draw certain conclusions concerning the mechanism of addition. Some of the more significant of those observations are the following:

1) Markownikoff's Rule.

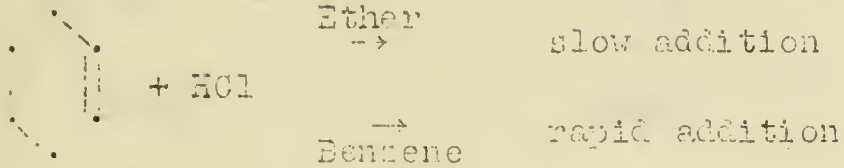
In general terms the rule may be stated as follows: When an unsymmetrical reagent adds to a carbon-carbon double bond, the more negative fragment appears on the carbon atom carrying the smaller number of hydrogen atoms.

2) When an addition such as a bromination is carried out in the presence of an anion other than the bromide ion, that anion may appear in the final product.



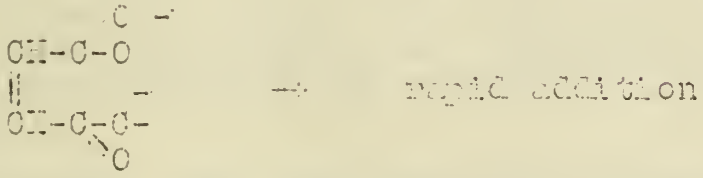
$$Br_2 + \;>C{=}C< \;\xrightarrow[NaCl]{H_2O}\; -\underset{Br}{\overset{|}{C}}-\underset{Cl}{\overset{|}{C}}-$$

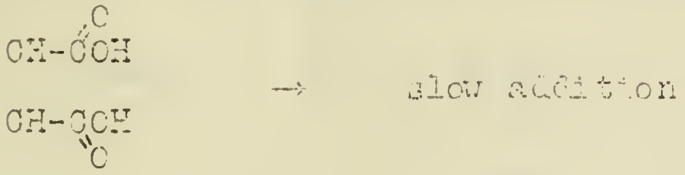
3) Solvents which are known to form oxonium salts with acids retard the addition of hydrogen halides.



4) The addition of HBr to a double bond is accelerated by the presence of $FeBr_3$.

5) The addition to a double bond is facilitated by the presence of a negative charge in the molecule and is hindered by a positive charge.





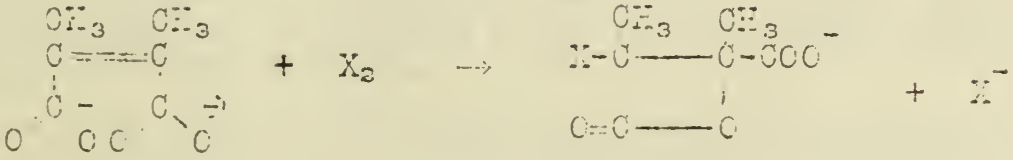
$H_2C=CHCH_2\overset{+}{N}R_3$ → not reactive

6) Addition to the carbon-carbon double bond is facilitated by electron releasing groups.

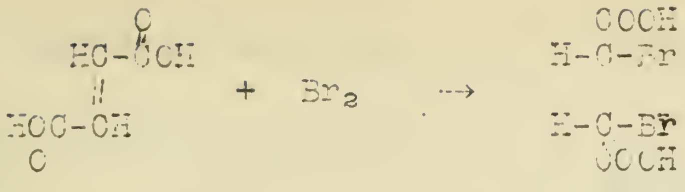
(Relative rates of reaction)

$Me_2C=CMe_2$	$MeCH=CH_2$	$H_2C=CH_2$	$MeCH=CHCOOH$	$CHBr=CH_2$
14.0	2.03	1.00	0.26	slow

7) The addition of halogens to a substituted acid results in lactone formation.



8) An addition to a trans olefin yields a meso product and addition to a cis olefin leads to a racemic modification.



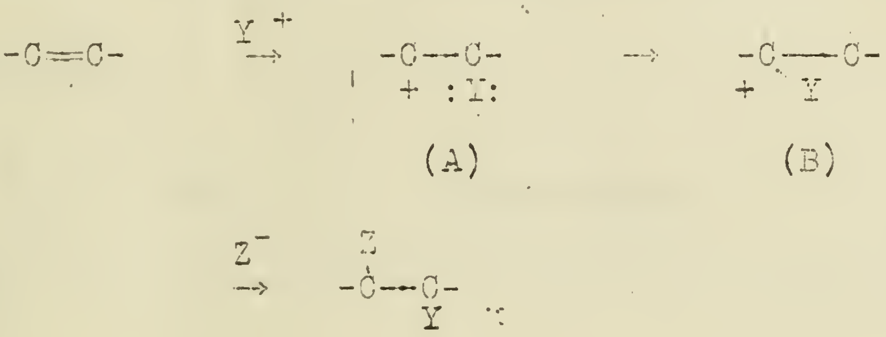
"trans"   "meso"

Deductions from the Experimental Data - Mechanism of Addition to Carbon-Carbon Double Bonds.

From the above experimental observations, we may infer the following:

Addition to the double bond occurs in two stages (2,7)- initial addition by a positive fragment (3,4,5,6,7), with the formation of a cyclic intermediate (6), followed by a rearward attack on the cyclic intermediate by the negative fragment of the attacking substance (8).

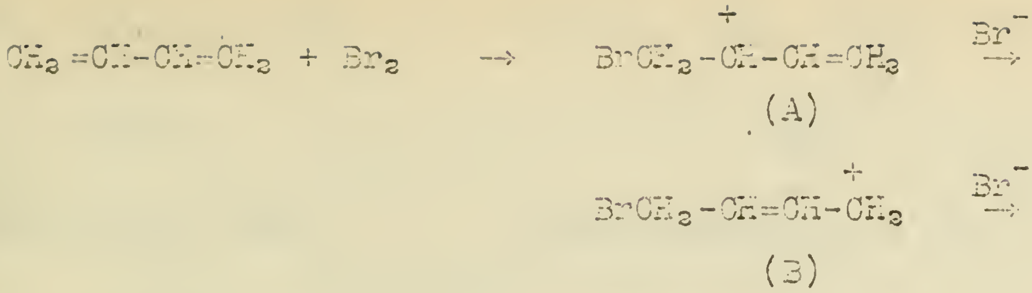
Schematically, the mechanism may be represented as follows:



In the case of addition of bromine to an olefin, formation of a cyclic bromonium intermediate is indicated by the fact that cis olefins lead to racemic dibromides, while trans olefins lead to meso. This could easily be explained by a displacement on B. If an intermediate carbonium ion were attacked by the bromide ion without first forming the cyclic bromonium intermediate (as in A), then both cis and trans olefins would yield the same dibromide.

In example 2 (above), an anion in the reaction mixture is likewise capable of a nucleophilic displacement on the cyclic intermediate and hence may appear in the final product. In example (7), rearward attack of the carbonyl ion on the cyclic intermediate would give the indicated product.

In the addition of bromine to a conjugated system such as butadiene, both 1,2 and 1,4 addition products can occur, depending upon whether the reaction proceeded through the form A or B below. Since form A is normally stabilized by the three-membered ring, **(as in (B))** it is to be expected that 1,2 addition will occur at low temperatures in non-polar media, while higher temperatures and polar solvents should favor addition to the ends of the conjugated system.



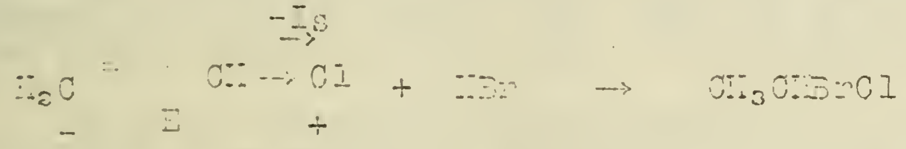
$$CH_2{=}CH{-}CH{=}CH_2 + Br_2 \longrightarrow BrCH_2{-}\overset{+}{C}H{-}CH{=}CH_2 \xrightarrow{Br^-} \quad (A)$$

$$BrCH_2{-}CH{=}CH{-}\overset{+}{C}H_2 \xrightarrow{Br^-} \quad (B)$$

Orienting Effect of Substituents on Carbon Atoms.

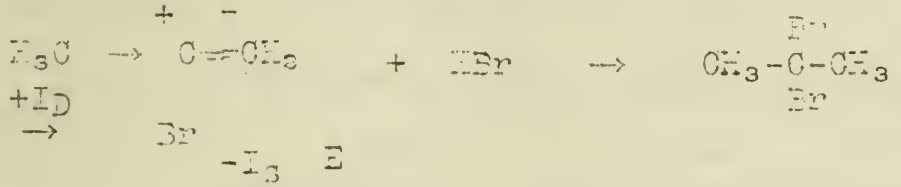
The following examples of the addition of HBr to olefins will serve to illustrate the electrical effects of various substituents:

1.



$$\underset{-}{H_2C} \overset{=}{\underset{E}{}} CH \overset{\xrightarrow{-I_s}}{\longrightarrow} \underset{+}{Cl} + HBr \longrightarrow CH_3CHBrCl$$

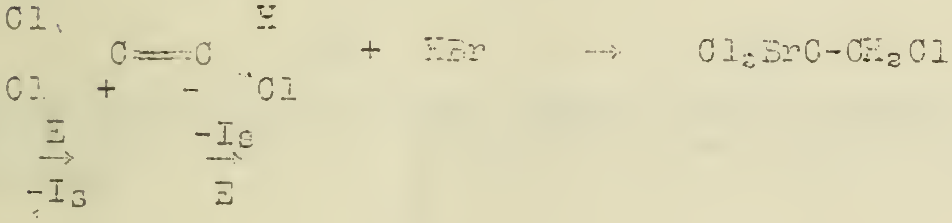
2.



$$\underset{\xrightarrow{+I_D}}{H_3C} \longrightarrow \overset{+}{C}{=}\overset{-}{C}H_2 + HBr \longrightarrow CH_3{-}\underset{Br}{\overset{Br}{C}}{-}CH_3$$

$$Br \quad -I_s \quad E$$

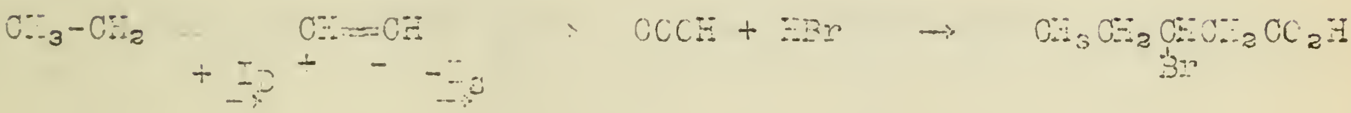
3.



$$\begin{matrix}Cl\\Cl\end{matrix}\overset{+}{C}{=}\overset{-}{C}\begin{matrix}H\\Cl\end{matrix} + HBr \longrightarrow Cl_2BrC{-}CH_2Cl$$

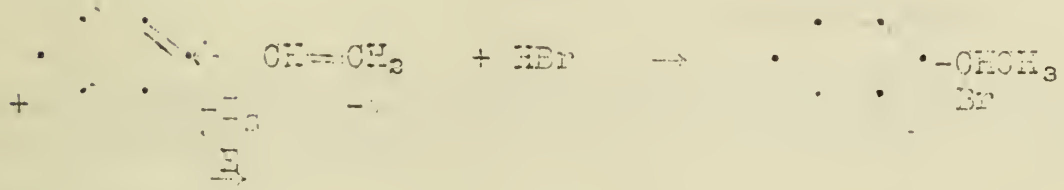
$$\underset{-I_s}{\xrightarrow{E}} \qquad \underset{E}{\xrightarrow{-I_s}}$$

4.



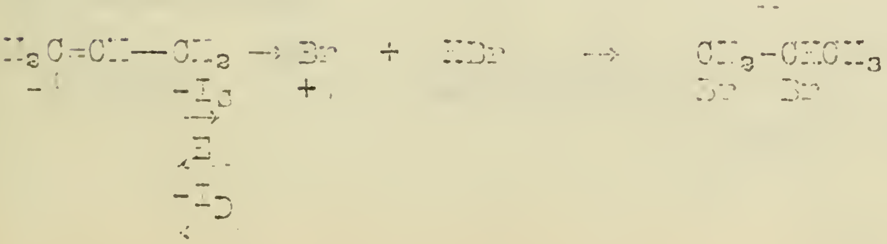
$$CH_3{-}CH_2 \underset{\xrightarrow{+I_D}}{\longrightarrow} \overset{+}{C}H{=}\overset{-}{C}H \underset{\xrightarrow{-I_s}}{\longrightarrow} COOH + HBr \longrightarrow CH_3CH_2\underset{Br}{C}HCH_2CO_2H$$

5.



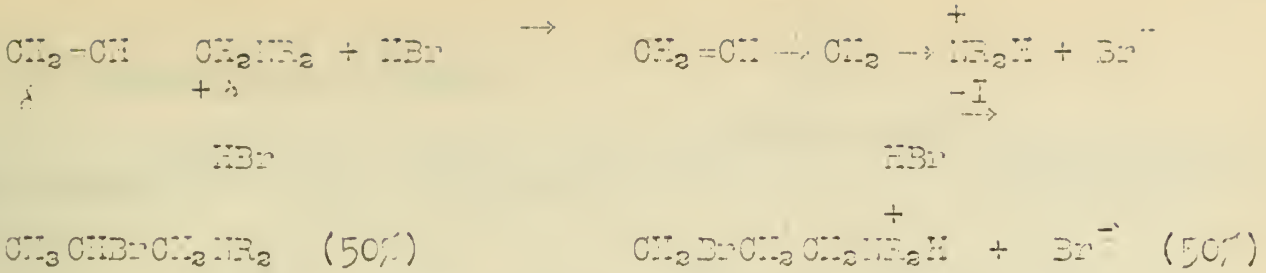
$$\overset{+}{}\quad \underset{\underset{\xrightarrow{E}}{-I_s}}{\longrightarrow} CH{=}\overset{-}{C}H_2 + HBr \longrightarrow {-}\underset{Br}{C}HCH_3$$

6.



$$\underset{-}{H_2C}{=}CH{-}\underset{\substack{-I_s\\ \longrightarrow\\ E\\ -I_D}}{CH_2} \longrightarrow \underset{+}{Br} + HBr \longrightarrow \underset{Br}{CH_2}{-}\underset{Br}{C}HCH_3$$

7.



$$CH_2{=}CH\;CH_2NR_2 + HBr \longrightarrow CH_2{=}CH \rightarrow CH_2 \rightarrow \overset{+}{N}R_2H + Br^-$$

$$\downarrow HBr \qquad\qquad \downarrow HBr$$

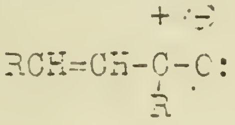
$$CH_3CHBrCH_2NR_2 \;(50\%) \qquad CH_2BrCH_2CH_2\overset{+}{N}R_2H + Br^- \;(50\%)$$

Nucleophilic Additions.

The addition reactions which have been discussed thus far have involved an electrophilic attack on the double bond. Some substituents, however, can so alter the normal availability of electrons in double bonds that attack may be initiated by a nucleophilic reagent such as NH_3, OEt^-, etc. This is particularly noticeable when groups such as cyano, nitro, or sulfone are present.

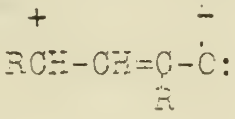
As in the electrophilic addition of HCl to acrylic acid, where $ClCH_2CH_2CO_2H$ is obtained, nucleophilic agents show a tendency to attack preferentially the end of a conjugated system.

Thus, of the two mesomeric forms contributing to the mesomeric hybrid



$$RCH{=}CH{-}\underset{R}{\overset{+}{C}}{-}\overset{-}{O}:$$

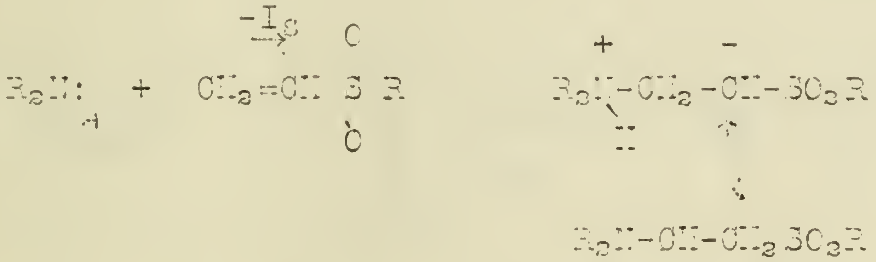
and



$$R\overset{+}{C}H{-}CH{=}\underset{R}{C}{-}\overset{-}{O}:$$

(A) (B)

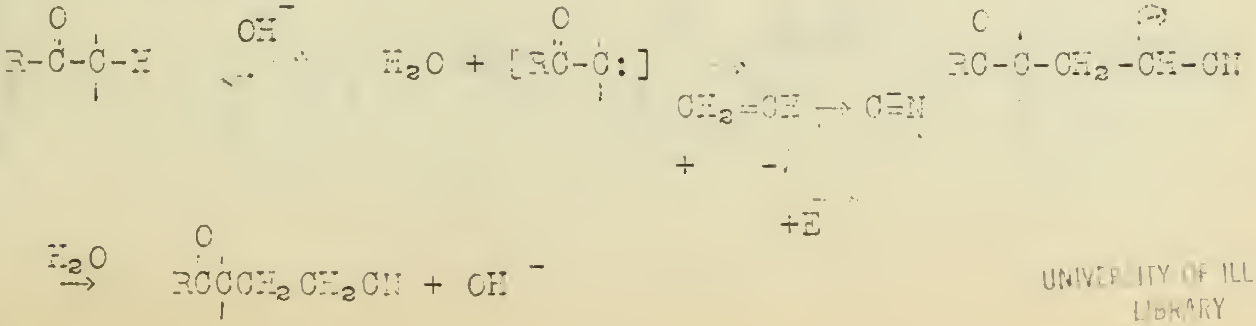
form B seems to be the one through which reaction occurs. An example of this type of reaction is the addition of amines to vinyl sulfones.



$$R_2N: + CH_2{=}CH\overset{-I_s}{\rightarrow}\underset{O}{\overset{O}{S}}R \longrightarrow R_2\overset{+}{N}{-}CH_2{-}\overset{-}{C}H{-}SO_2R \longrightarrow R_2N{-}CH{-}CH_2SO_2R$$

Cyanoethylation and the Michael Condensation are other examples of nucleophilic attack:

Cyanoethylation



$$R{-}\overset{O}{\overset{\|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H \xrightarrow{OH^-} H_2O + [R\overset{O}{\overset{\|}{C}}{-}\underset{|}{\overset{|}{C}}:] \xrightarrow{CH_2{=}CH \rightarrow C{\equiv}N} R\overset{O}{\overset{\|}{C}}{-}\overset{|}{C}{-}CH_2{-}\overset{-}{C}H{-}CN$$

$$\xrightarrow{H_2O} R\overset{O}{\overset{\|}{C}}\underset{|}{C}CH_2CH_2CN + OH^-$$

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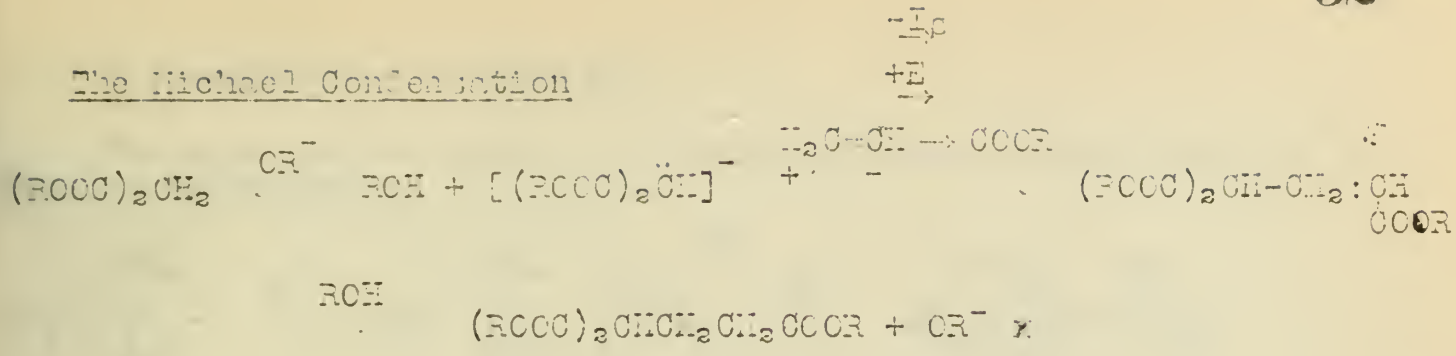
The Michael Condensation



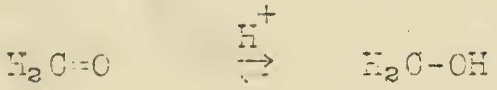
$$(ROOC)_2CH_2 \xrightarrow{OR^-} ROH + [(ROOC)_2\ddot{C}H]^- \xrightarrow[+\quad -]{\overset{-I_s}{\overset{+E}{}}\; H_2C{=}CH \rightarrow COOR} (ROOC)_2CH-CH_2:\overset{\cdot\cdot}{C}H-COOR$$

$$\xrightarrow{ROH} (ROOC)_2CHCH_2CH_2COOR + OR^-$$

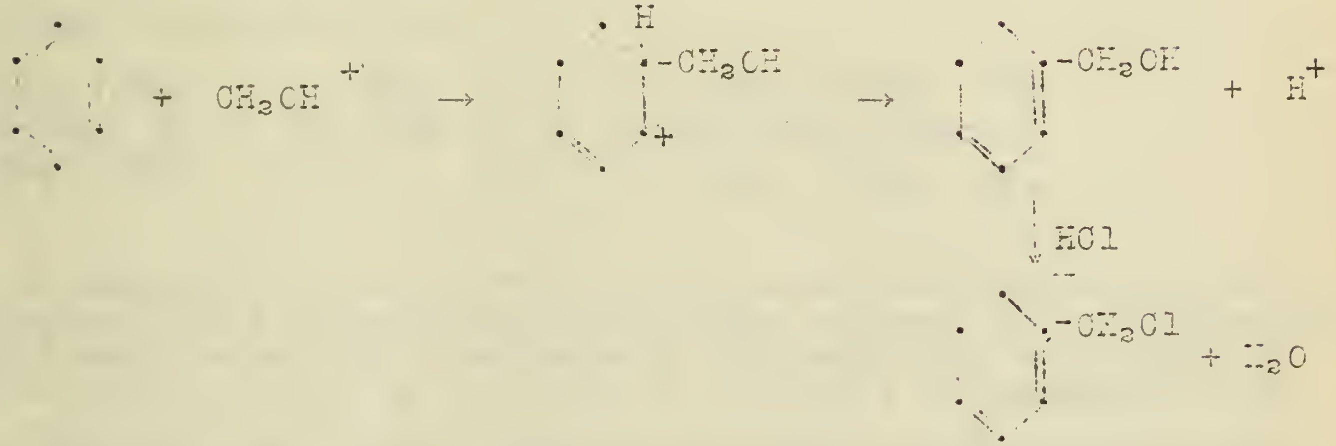
Examples of Related Addition Reactions

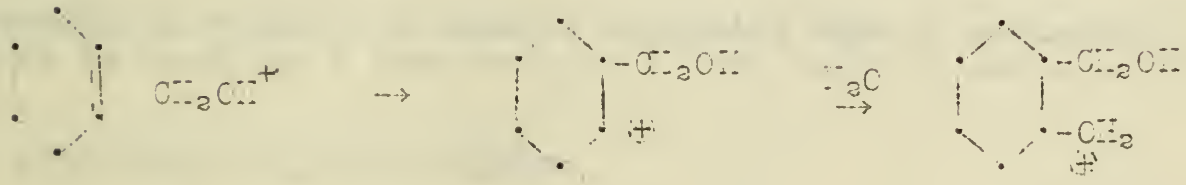
A. Addition of formaldehyde.

Chloromethylation and the Prins reaction are closely related electrophilic reactions.

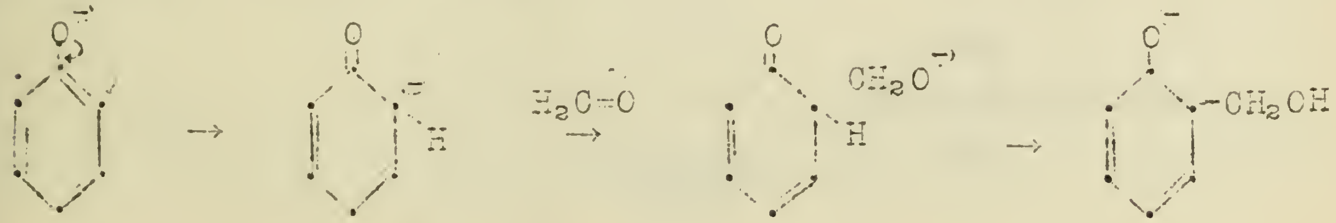


$$H_2C{=}O \overset{H^+}{\rightleftarrows} H_2C-OH$$


+ CH₂OH⁺
H
-CH₂OH
+
-CH₂OH
+ H⁺
HCl
-CH₂Cl
+ H₂O

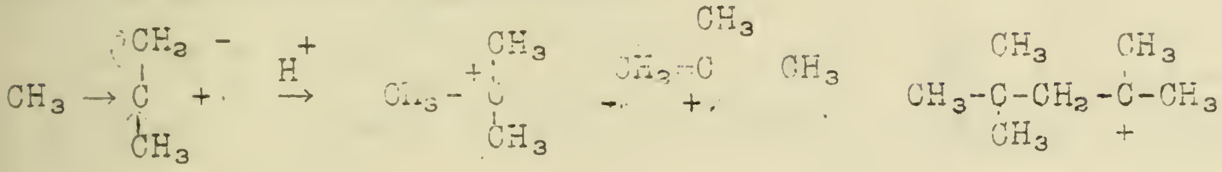

CH₂OH⁺
-CH₂OH
+
-H₂O
-CH₂OH
-CH₂
+

The base catalyzed condensation of phenols with formaldehyde, on the other hand, is an example of the nucleophilic addition of the phenolate ion to formaldehyde. (To be discussed under carbanion addition to carbonyl groups.)

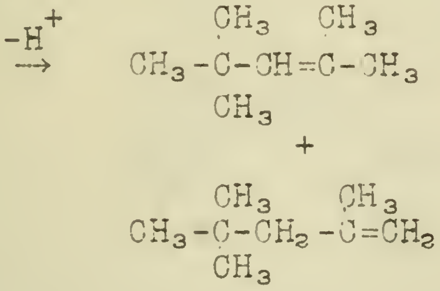

O⁻
O
-
H
H₂C=O
O
CH₂O⁻
H
O⁻
-CH₂OH

B. Polymerization of olefins.

The acid polymerization of isobutylene can be explained by a similar mechanism.

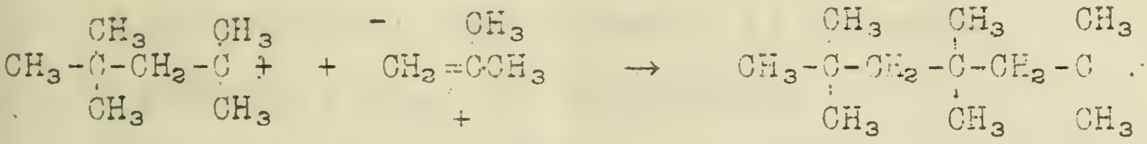


$$\mathrm{CH_3 \rightarrow \underset{CH_3}{\overset{\overset{-}{CH_2}}{C}} + \xrightarrow{H^+} CH_3-\underset{CH_3}{\overset{CH_3}{\overset{+}{C}}} \quad \overset{CH_3}{\underset{-}{CH_2}=\underset{+}{C}} \quad CH_3 \qquad CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{+}{\overset{CH_3}{C}}-CH_3}$$



$$\mathrm{\xrightarrow{-H^+} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH=\overset{CH_3}{C}-CH_3 \quad + \quad CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\overset{CH_3}{C}=CH_2}$$

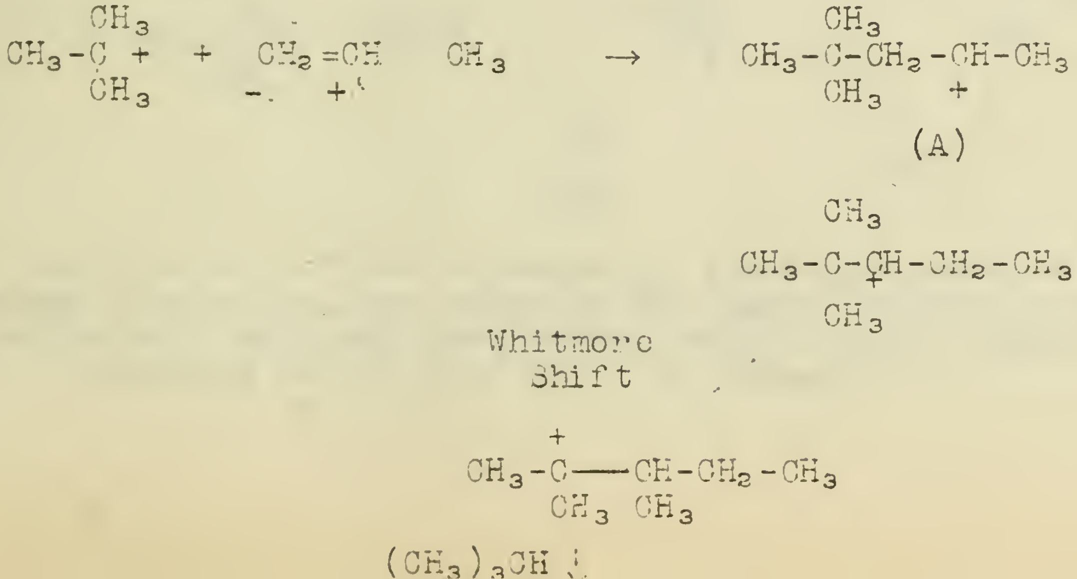
or further polymerization:



$$\mathrm{CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}{}^{+} + \overset{-}{CH_2}=\underset{+}{\overset{CH_3}{C}}CH_3 \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}}$$

In connection with the nucleophilic and electrophilic activity of olefins, it is interesting to note that styrene may be polymerized to give head-to-tail type polymers by electrophilic, nucleophilic, or free radical reagents. Presumably an active intermediate of the type $[\text{Ø}\underset{Z}{C}H\text{-}CH_2R]$ is formed, where Z represents a carbonium when an electrophilic reagent is used; a carbanion when a nucleophilic reagent is used; or a free radical in the case of peroxide attack.

C. Alkylation of Isoparaffins.



$$\mathrm{CH_3-\underset{CH_3}{\overset{CH_3}{C}}{}^{+} + \underset{-}{CH_2}=\underset{+}{CH} \quad CH_3 \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{+}{CH}-CH_3}$$

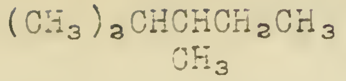
(A)

$$\mathrm{CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{+}{CH}-CH_2-CH_3}$$

Whitmore Shift

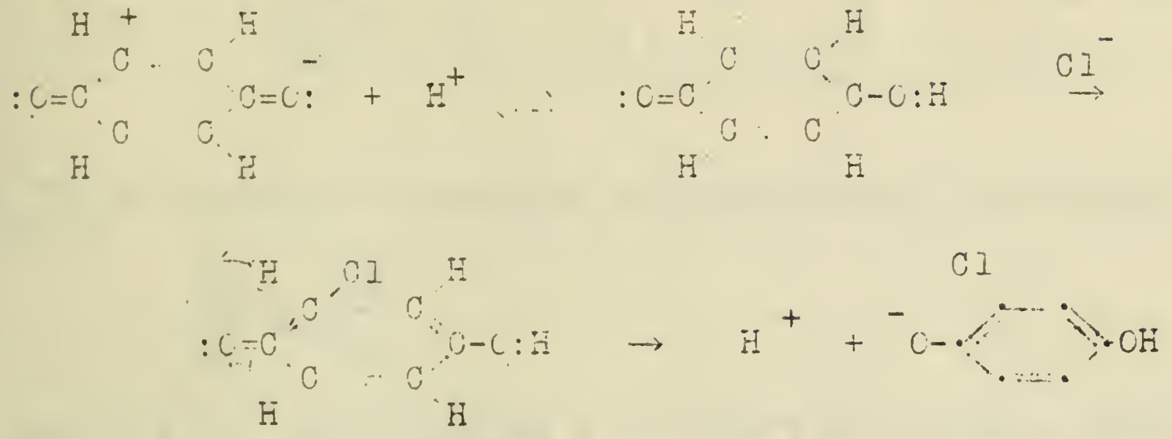
$$\mathrm{CH_3-\underset{CH_3}{\overset{+}{C}}-\underset{CH_3}{CH}-CH_2-CH_3}$$

$$\mathrm{(CH_3)_3CH}$$



$$(CH_3)_2CH\underset{CH_3}{C}HCH_2CH_3$$

D. 1,4 Addition to quinones.

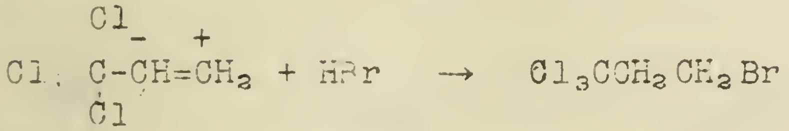


Anomalies.

Experimentally, the following is observed:

1. $Cl_3CCH{=}CH_2 + HBr \rightarrow Cl_3CCHBrCH_3$

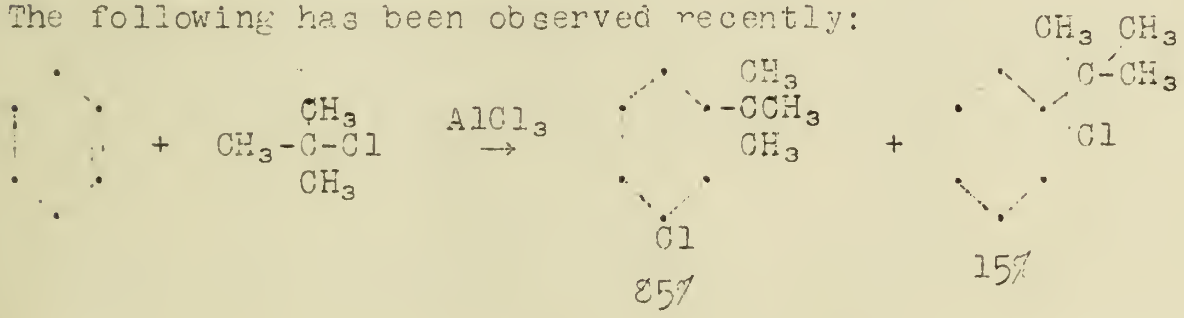
One would expect, however, the following mode of addition:



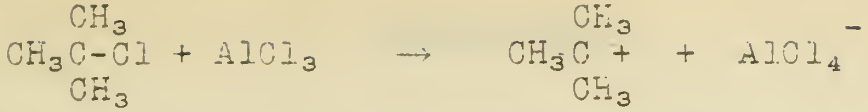
$$Cl\overset{Cl}{\underset{Cl}{\overset{-}{C}}}\overset{+}{-}CH{=}CH_2 + HBr \rightarrow Cl_3CCH_2CH_2Br$$

2. Maleate and fumarate ions both give meso dibromosuccinic acid by addition of bromine. This is contrary to the expected trans addition, as discussed above.

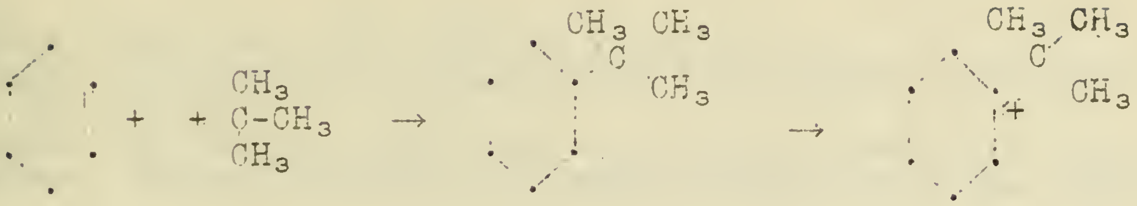
3. The following has been observed recently:



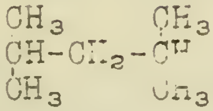
It would be reasonable to expect 1,1 and 1,2 addition to the cyclohexene double bond but actually the major product is the 1,3 addition product, entirely unexpected, while a small amount of 1,1 product is obtained and none of the 1,2 product.



$$\begin{matrix} & CH_3 & \\ CH_3 & C & -Cl \\ & CH_3 & \end{matrix} + AlCl_3 \longrightarrow \begin{matrix} & CH_3 & \\ CH_3 & C & + \\ & CH_3 & \end{matrix} + AlCl_4^-$$

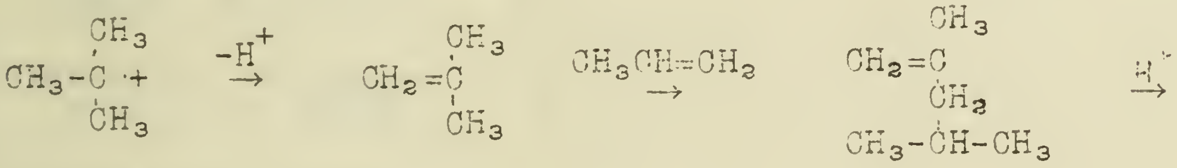


4. In the alkylation of propylene with isobutane the principal product is

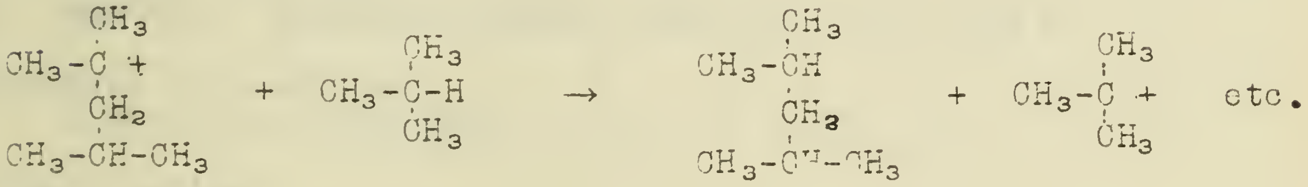


$$\begin{matrix} CH_3 & & CH_3 \\ CH & -CH_2- & CH \\ CH_3 & & CH_3 \end{matrix}$$

This may be interpreted as a 1,3 shift of a methyl group (see formula (A) under part C of the preceeding section) or as indicating a change in the mechanism. According to the latter point of view the reaction may be looked at as an olefin condensation reaction.



$$\begin{matrix} & CH_3 & \\ CH_3- & C & + \\ & CH_3 & \end{matrix} \xrightarrow{-H^+} \begin{matrix} & CH_3 \\ CH_2= & C \\ & CH_3 \end{matrix} \xrightarrow{CH_3CH=CH_2} \begin{matrix} & CH_3 & \\ CH_2= & C & \\ & CH_2 & \\ CH_3- & CH & -CH_3 \end{matrix} \xrightarrow{H^+}$$



$$\begin{matrix} & CH_3 & \\ CH_3- & C & + \\ & CH_2 & \\ CH_3- & CH & -CH_3 \end{matrix} + \begin{matrix} & CH_3 & \\ CH_3- & C & -H \\ & CH_3 & \end{matrix} \longrightarrow \begin{matrix} & CH_3 & \\ CH_3- & CH & \\ & CH_2 & \\ CH_3- & CH & -CH_3 \end{matrix} + \begin{matrix} & CH_3 & \\ CH_3- & C & + \\ & CH_3 & \end{matrix} \quad \text{etc.}$$

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Addition of HX:
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Addition of X_2:
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Orientation:
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Addition of CH_2O:
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Nucleophilic Addition:
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Addition to Quinones:
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Carbonium Ion Addition:
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Polymerization:
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Addition to a Conjugated System:
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Resonance Effects on Additions:
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Stereoisomerism of Additions:
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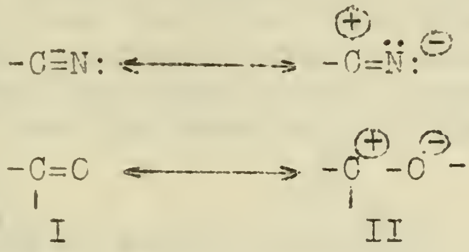
Hammett, pp. 147-149.

General.--In discussing simple addition reactions to carbon-oxygen and carbon-nitrogen bonds it is important to observe that there is not only a significant contribution of form II to the resonance hybrid of I and II (in which form the carbonyl group exists) but also that under the influence of a reagent an electromeric shift in the direction of II may occur so as to further increase the electronegative character of oxygen or nitrogen.

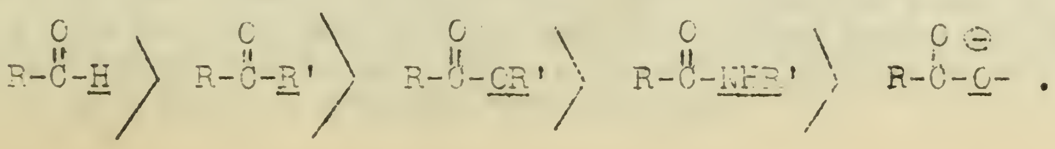


Since there are in the extreme case (II) both an atom with a completely filled valence shell (oxygen or nitrogen) and an atom with only six electrons about it (carbon), there should be cases in which the carbonyl group acts as a nucleophilic reagent and others in which it behaves as an electrophilic reagent. It is interesting that in most of its addition reactions the slow step appears to be addition to the carbonyl carbon atom. It has therefore become customary to discuss the effect of substitutents on the carbonyl group from the point of view that those groups which increase the positive character of the carbonyl carbon atom increase accordingly the reactivity of the group. Certainly this is an important simplification and one which it is usually valid to make. That it is not always valid can be seen from the following table which shows the complete lack of correlation between the positive character of the carbonyl group and the extent of cyanohydrin formation.

Effect of Substitutents on the Extent of the Reaction of HCN with Carbonyl Compounds

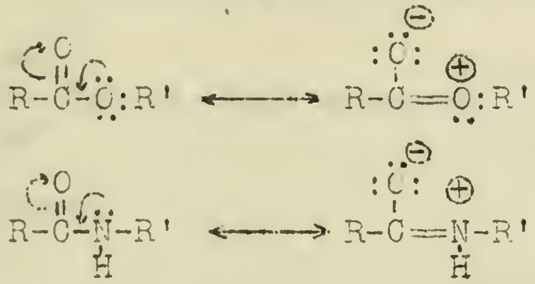
Compound	K x 10^2
dimethyl ketone	3.05
methyl ethyl ketone	2.65
methyl isopropyl ketone	1.55
methyl-tert-butyl ketone	3.10
benzaldehyde	0.47
p-nitrobenzaldehyde	1.81
p-methoxybenzaldehyde	3.12
p-hydroxybenzaldehyde	7.66
p-dimethylaminobenzaldehyde	39.00

It is well known that the reactivity of a carbonyl group toward nucleophilic reagents decreases in the following order:

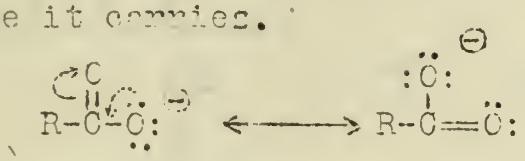


$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underline{H}} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underline{R'}} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underline{OR'}} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underline{NHR'}} > \mathrm{R{-}\overset{O^{\ominus}}{\overset{|}{C}}{-}\underline{O}{-}}\ .$$

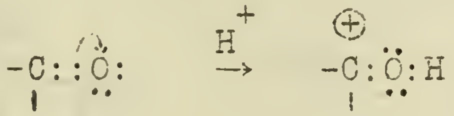
It can be seen that this is the order which would have been predicted from the electrical effects which are in operation if we assume that it is the decreasing positive character of the carbon atom of the carbonyl group which is responsible for the decreasing order of reactivity. The comparison here involves the relative electron release of the groups which are underlined. Because alkyl groups exhibit greater electron release than hydrogen, both by an inductomeric effect and by hyperconjugation, aldehydes will be more reactive toward nucleophilic reagents than ketones. In comparing ketones to esters and amides it can be seen that the latter two have an electron pair which can enter into a mesomeric and electromeric shift so as to decrease the positive charge on carbon.



Since nitrogen lies to the left of oxygen in the periodic system the +E and +M effects of -NHR' will be greater than those of -OR'. The carboxylate ion falls at the end of the list because of the unit negative charge it carries.



Since most additions to the carbon-oxygen double bond are nucleophilic, the presence of acid in the reaction mixture should catalyze the reaction. The addition of a proton to the carbonyl oxygen would render the adjoining carbon atom more electropositive.

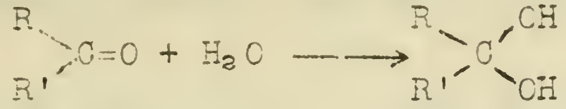


However, a nucleophilic reagent is a base itself and will react with the acid catalyst to form the conjugate acid of the original reagent, thus decreasing the concentration of one of the reactants.

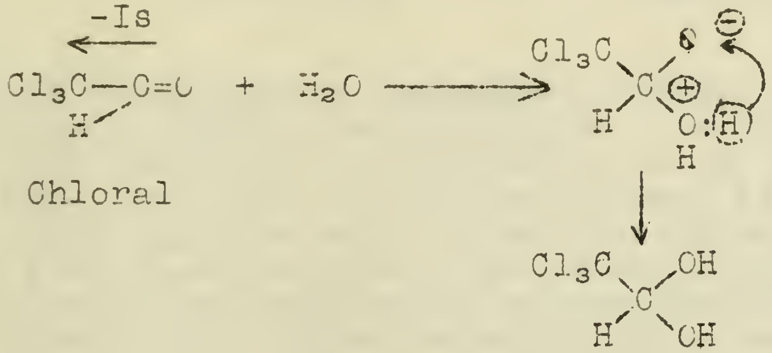
$$H^+ + A^- \rightleftharpoons HA$$

Since these effects operate in opposition it is clear that there will be an optimum pH for the rate of reaction above and below which the rate will decrease. This point can be illustrated with the cyanohydrin reaction. In strongly basic solution the carbonyl group is not activated and in strongly acidic solution the concentration of CN^- is low. The reaction therefore proceeds best at a pH of about 12. A similar maximum in the rate versus pH curve is observed with other addition reactions such as bisulfite addition and the addition of substituted ammonia derivatives.

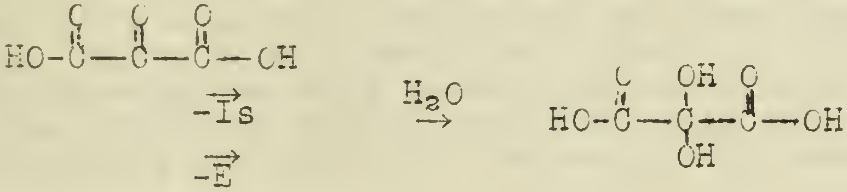
Hydration and Hemiacetal Formation.--Aldehydes and ketones, when dissolved in water, are presumably in equilibrium with their hydrates.



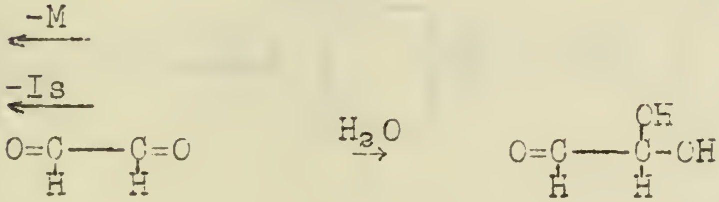
In most cases, however, these hydrates are too unstable to be isolated. However, when the reactivity of the carbonyl group is increased by attaching strong -Is or -M groups to it, it is expected that the stability of the hydrate will be increased. Thus chloral, mesoxalic acid and glyoxal form stable crystalline hydrates.



Chloral

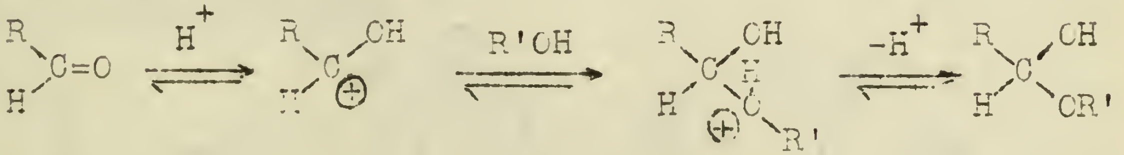


Mesoxalic acid



Glyoxal

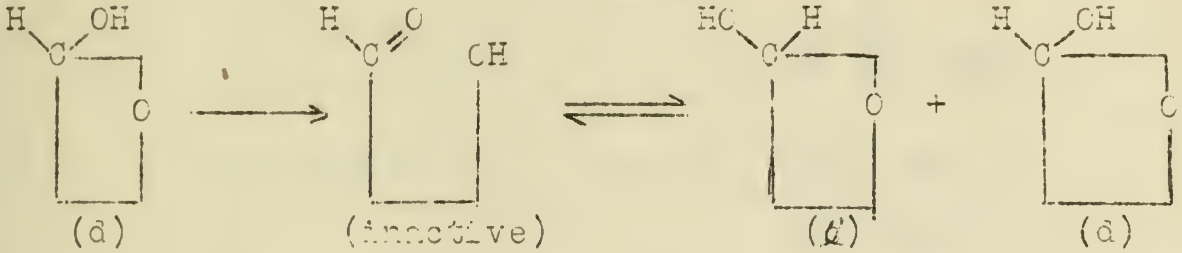
Hemiacetal formation, like hydration, is reversible and is catalyzed by acids.



The formation of acetals from hemiacetals will be discussed in a later seminar under "Etherification and Cleavage."

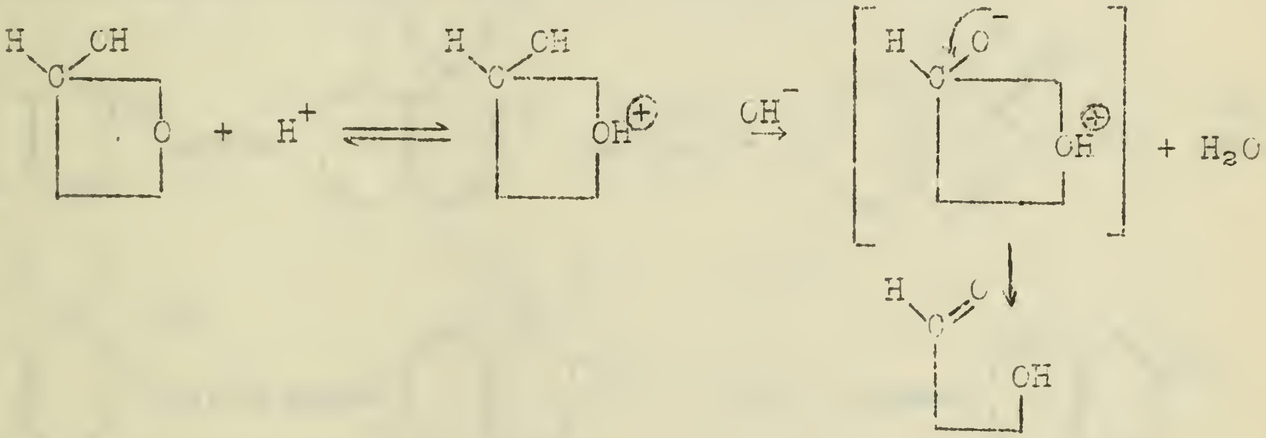
Since it has been pointed out that the hemiacetal form is in equilibrium with the carbonyl compound in alcohol, it is not surprising to find the phenomena of mutarotation in the sugar series.

The liberation of the free aldehyde from the internal hemiacetal form of the sugar destroys the optical activity of carbon and the reformation of the hemiacetal in either configuration of the aldehydic carbon results in a racemic mixture, at least so far as carbon 1 is concerned.

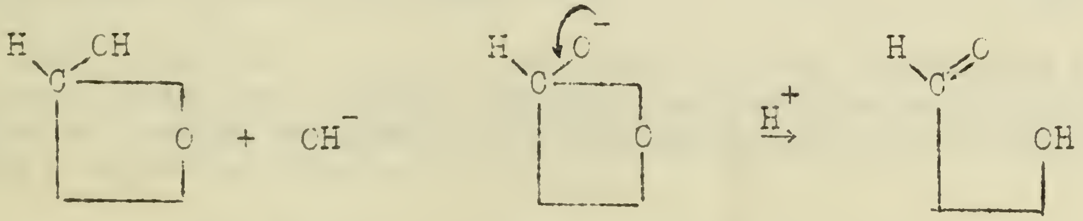


Insight into the mechanism of hemiacetal formation has been gained by a rather careful study of mutarotation. In this reaction both the aldehyde and the alcohol are attached to the same molecule and the rate of hydrolysis can be readily followed by optical methods. It has been found that the reaction exhibits general acid and general base catalysis but that neither alone is sufficient. Thus mutarotation is not observed in the case of tetramethylglucose when the reaction is carried out either in the strongly basic but weakly acidic solvent pyridine or in the strongly acidic and weakly basic solvent cresol. In a mixture of the two solvents the reaction proceeds rapidly. Since both an acid and a base are required for reaction it is to be expected that there again will be an optimum pH above and below which the rate of reaction will decrease. The mechanisms for hydrolysis in acidic and in basic media are shown below.

Hydrolysis in Acidic Solution:



Hydrolysis in Basic Solution:



Cyanohydrin Formation and Bisulfite Addition Products.--The formation of cyanohydrins and bisulfite addition products depend upon the addition of an anion, $:Y^-$, to the carbon of the carbonyl group. The following equations illustrate the mechanisms:

[illegible]

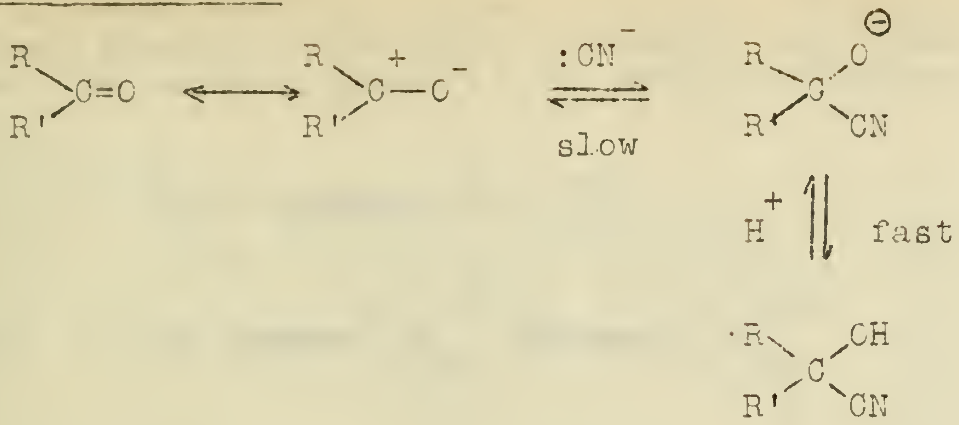
[illegible]

[illegible]

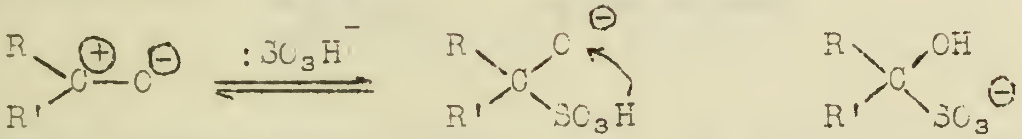
[illegible]

[illegible]

Cyanohydrin formation:

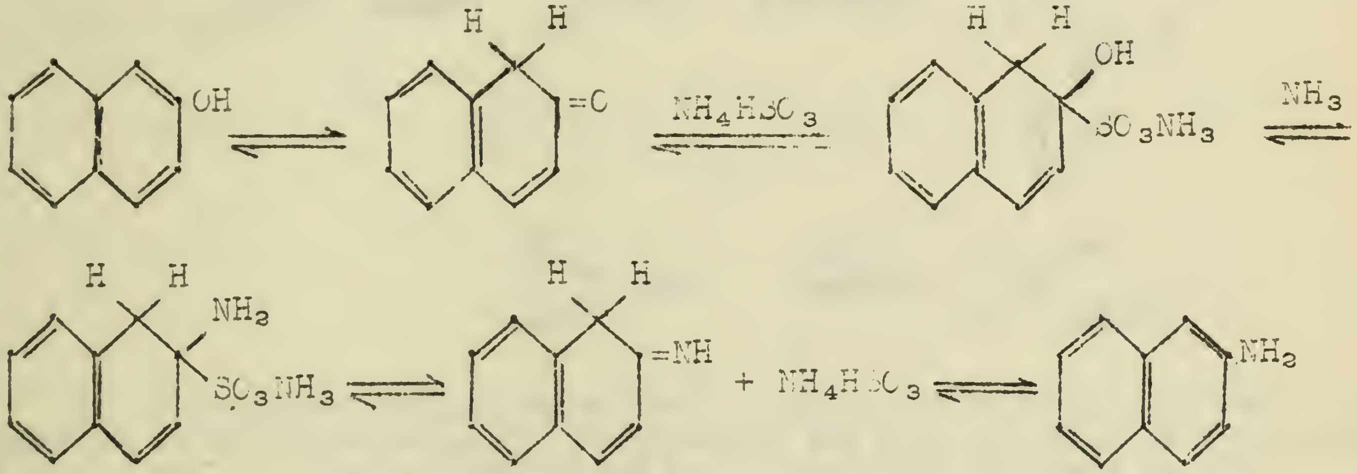


Bisulfite Addition:



The acid concentration in cyanohydrin formation is important, as high acidity, though catalyzing the addition reaction, will effectively remove CN^- as undissociated HCN. This molecule has been shown to be incapable of adding to the carbonyl group.

The Bucherer reaction appears to involve the intermediate formation of a bisulfite addition product followed by the replacement of the resulting hydroxyl group by an amino group. Subsequent hydrolysis establishes equilibrium between the amine and phenol. These steps may be represented by the following equilibria.

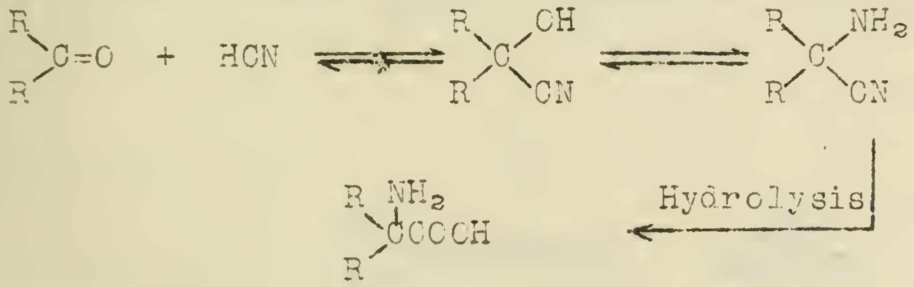


The essential step in the reaction, the replacement of the hydroxyl group by an amino group, has been demonstrated by the isolation of sodium aminomethyl sulfonate from the bisulfite addition product of formaldehyde.

$$HOCH_2-SO_3Na \quad \xrightarrow{NH_3} \quad H_2NCH_2SO_3Na$$

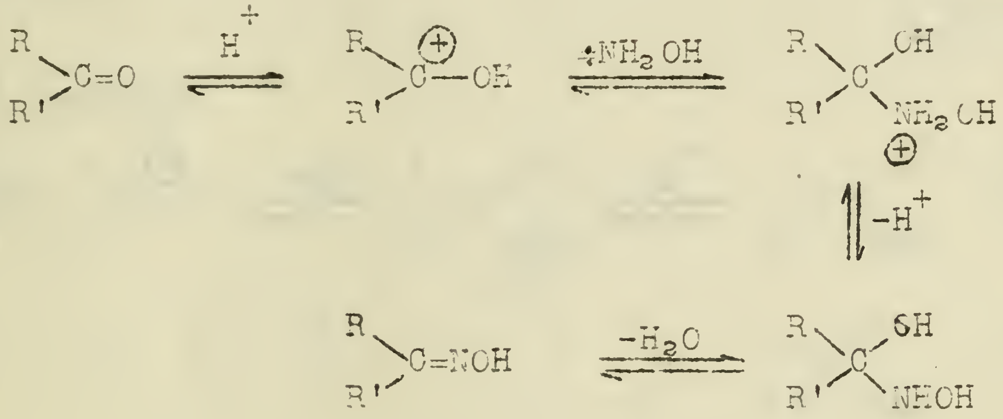
This is in accord with the general principle that electron attracting groups attached to the seat of reaction facilitate Sn_2 reactions. A similar displacement occurs in the Strecker synthesis of α-amino acids.

$$NH_4CN \rightleftharpoons NH_3 + HCN$$

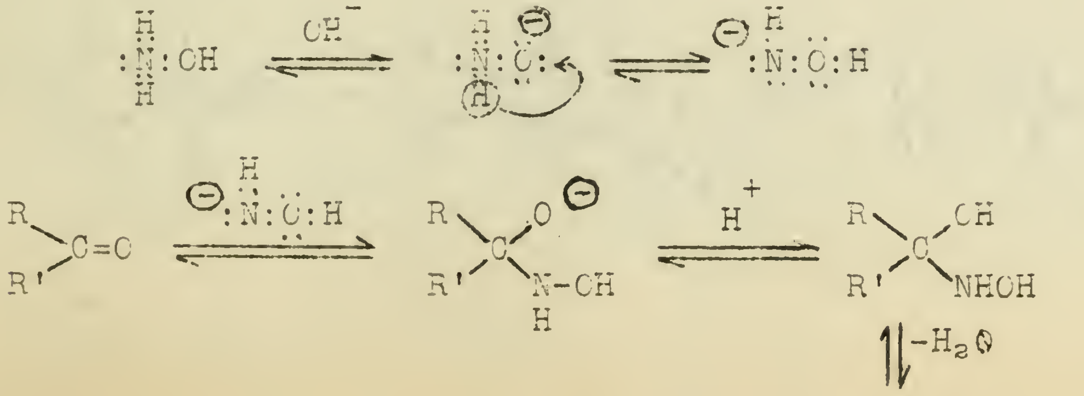


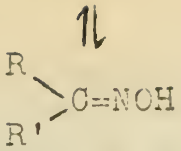
Ammonia Derivatives.--Ammonia and its derivatives add to the carbonyl group by essentially the same mechanism. As all these addition reactions are catalyzed by acid, the initial process presumably involves the addition of a proton to the oxygen of the carbonyl group; the free electron pair on the nitrogen atom of the ammonia derivative then adds to the positive carbon atom of the carbonyl group, followed by the elimination of a proton. In many cases, water then splits out from the resulting addition product.

1. Hydroxylamine.

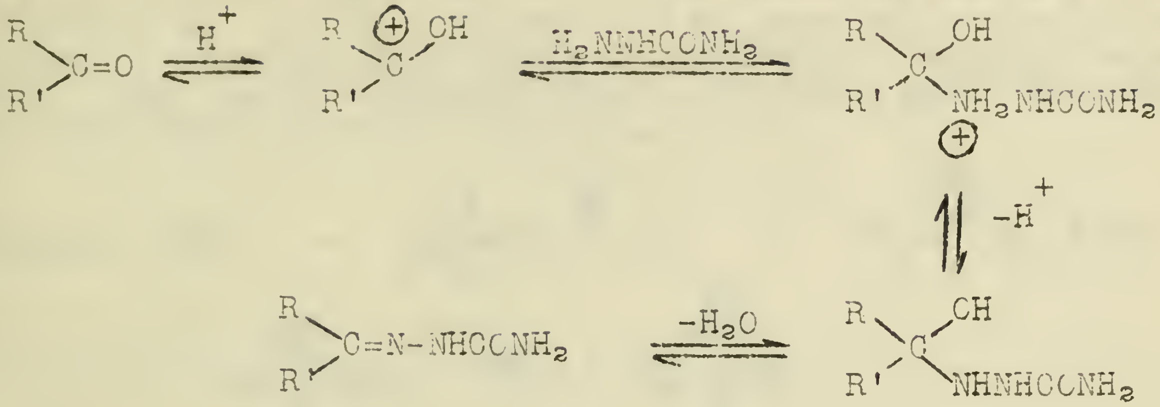


It is interesting to note that in strongly alkaline media, the reaction rate is increased. Presumably this is due to the formation of the H_2NO^- ion which adds readily to carbonyl systems as CN^-, SO_3H^- and R^- do.

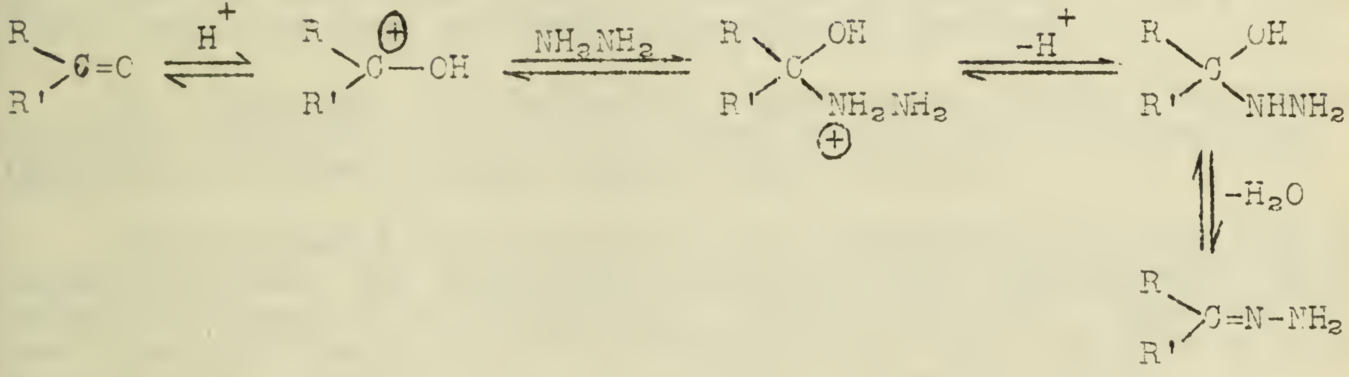




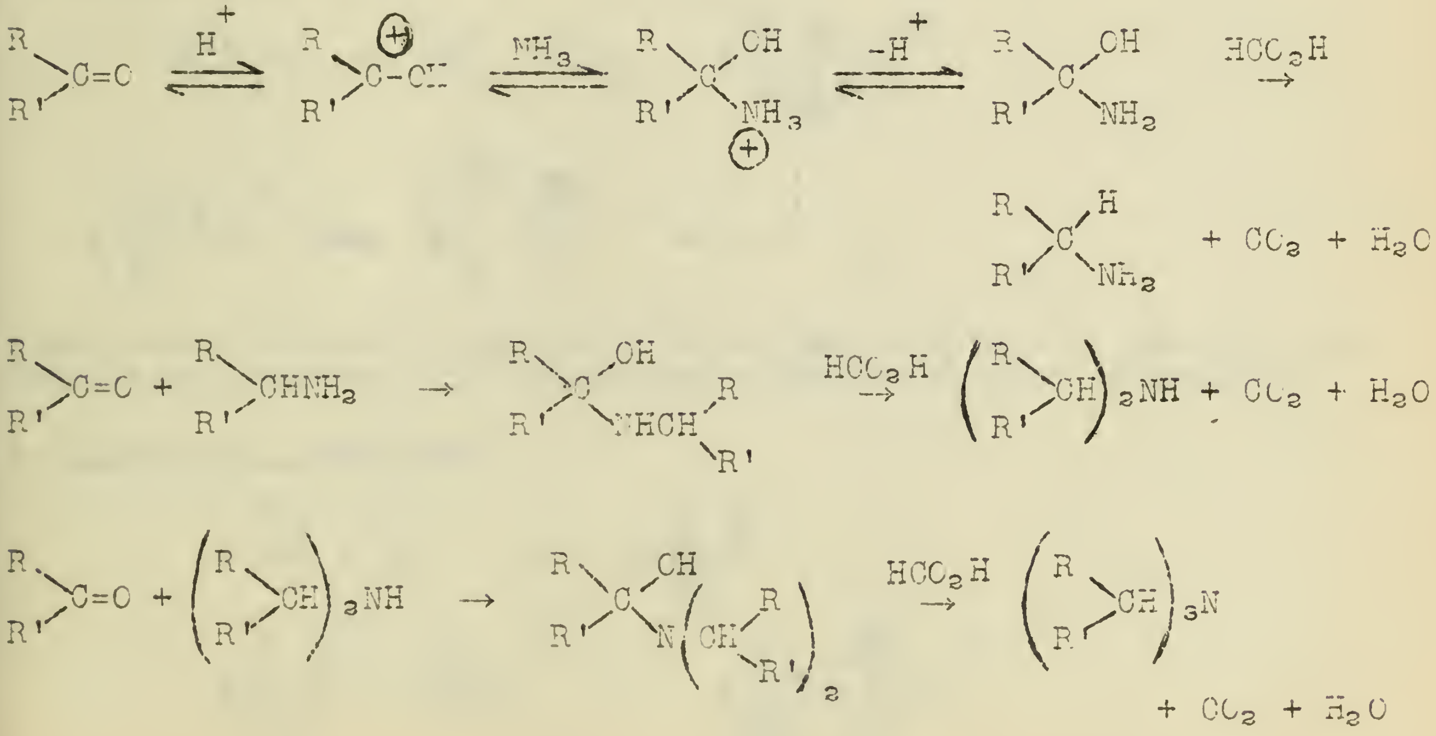
2. Semicarbazide.



3. Hydrazine.

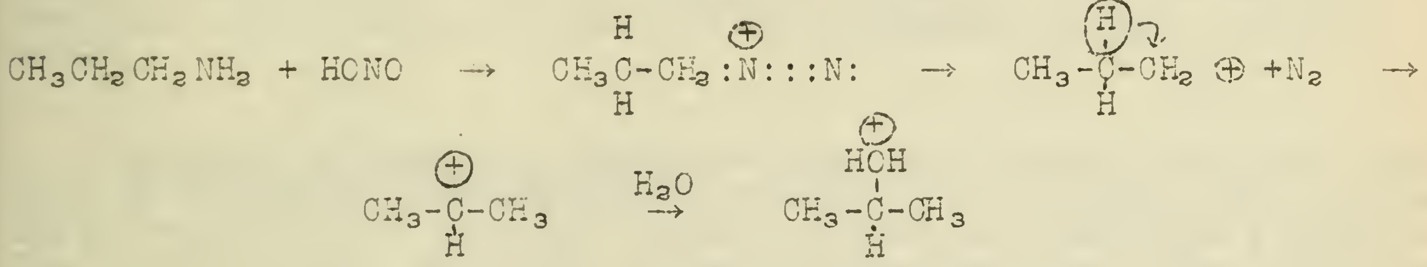


4. Leuckart Reaction.



Addition of Hydride Ion.--Although hydride ions and their reactions are well known to inorganic chemists, the postulation of the transfer of a hydrogen atom with a pair of electrons is frequently met with some skepticism on the part of many organic chemists.

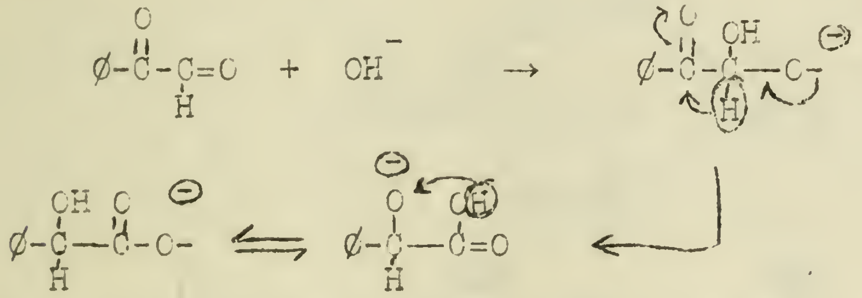
In acid solution there can be little doubt that such a transfer occurs frequently. In the formation of an n-propyl carbonium ion by the reaction of nitrous acid with n-propyl amine, isopropyl alcohol is formed. This can be interpreted as a Whitmore shift involving a hydrogen atom with a pair of electrons.



By a similar mechanism isopropyl benzene is obtained from a Friedel-Crafts reaction with n-propyl chloride and benzene.

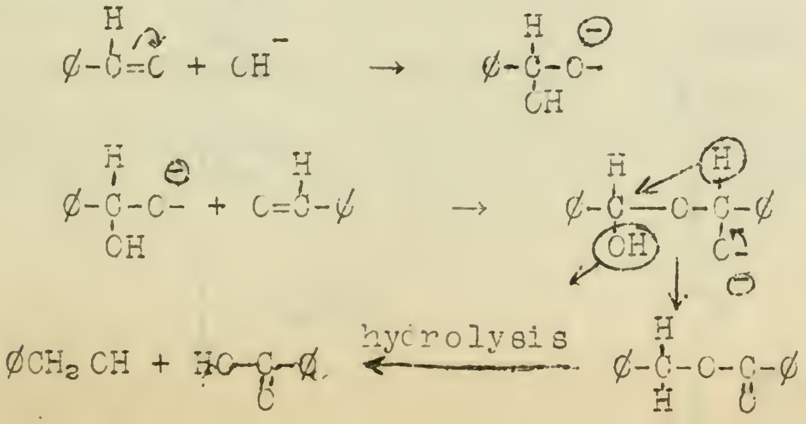
The alkylation of olefins by isoparaffins involves the intermolecular transfer of a hydrogen atom with a pair of electrons (Addition to Carbon-Carbon Double Bonds, p. 9).

In basic solution the evidence is convincing at least for one transformation. The Cannizzaro reaction with phenylglyoxal is first order with respect to the glyoxal and hydroxyl ion. This can only mean that the transfer of the hydrogen atom with its pair of electrons to the carbonyl group takes place intramolecularly.

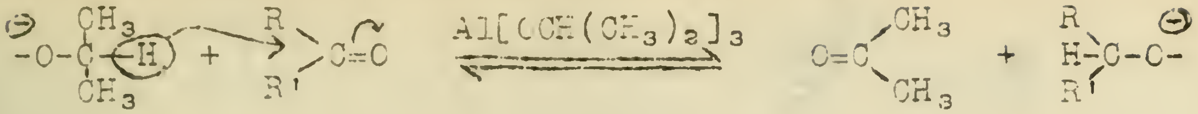


Other reactions which may have mechanisms similar to this are the Cannizzaro reaction and the Meerwein-Pondorf-Verley reduction.

A. Cannizzaro Reaction.

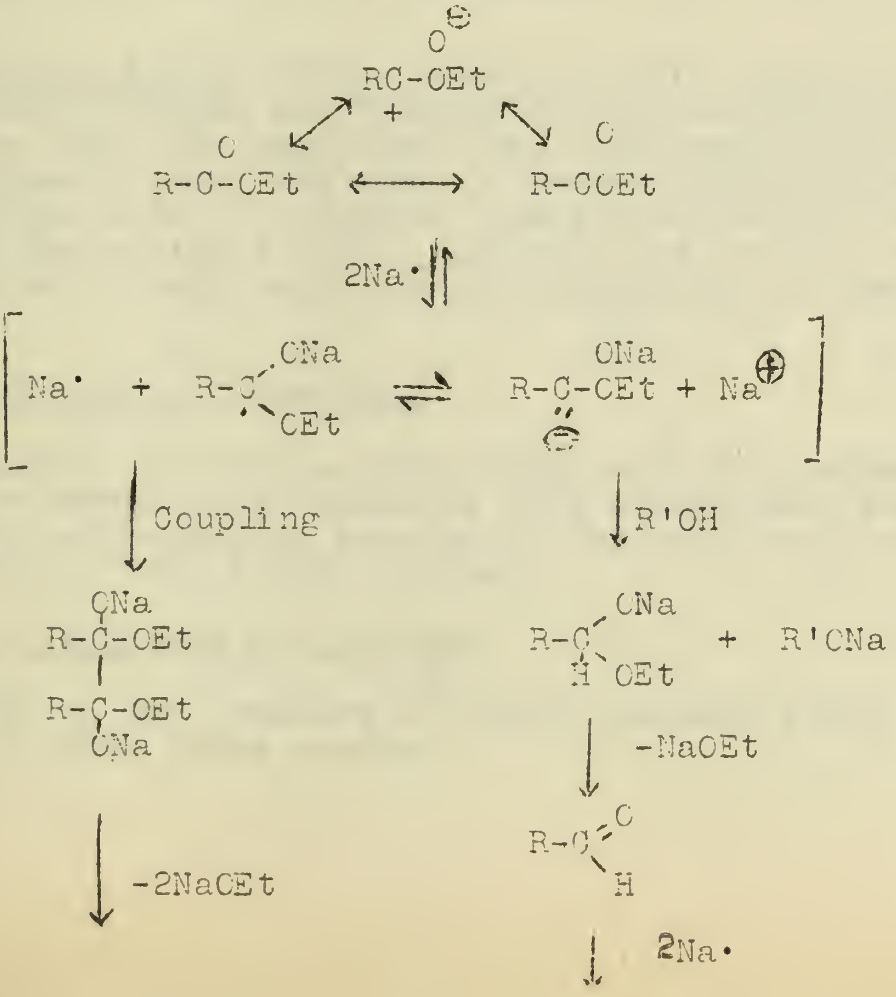


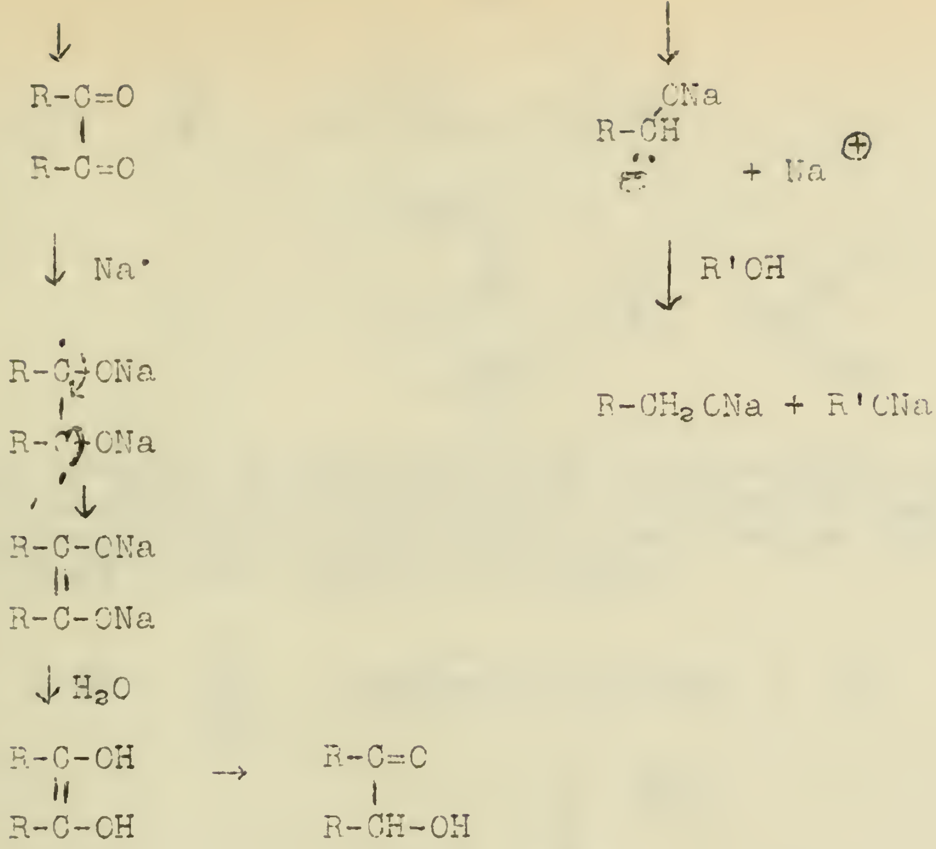
B. Meerwein-Ponndorf-Verley Reduction.



In connection with this mechanism it should be observed that since olefinic bonds are usually attacked by electrophilic reagents, the Meerwein-Ponndorf-Verley reduction should attack only the carbonyl group of an unsaturated carbonyl compound. This is actually the case both in this reaction and in reactions carried out with $LiAlH_4$.

Addition of Sodium to Esters.--Into this category fall the reduction of esters to alcohols and the formation of acyloins from esters. These reactions are closely related and will be considered together. The original ester reduction process of Bouveault and Blanc consisted of the addition of sodium to an ethanolic solution of the ester, and was thought to be brought about by the action of "nascent hydrogen." It has recently been found that the reaction of sodium with ethanol is a side reaction which wastes sodium. A mechanism which has recently been postulated involves the direct addition of sodium to the carbonyl group followed by reaction of this adduct with the alcohol present. In cases where the alcohol reacts too slowly with the sodium adduct (tertiary alcohols) or where no alcohol is present, a free radical type reaction takes place and leads to a coupling of two ester molecules with ultimate formation of an acyloin. These reactions may be illustrated as follows:





Commercial application of the reduction of esters utilizes secondary alcohols, such as methyl isobutyl carbinol, which react rather slowly with sodium but rapidly enough with the sodium adduct to keep acyloin formation from dominating the reaction.

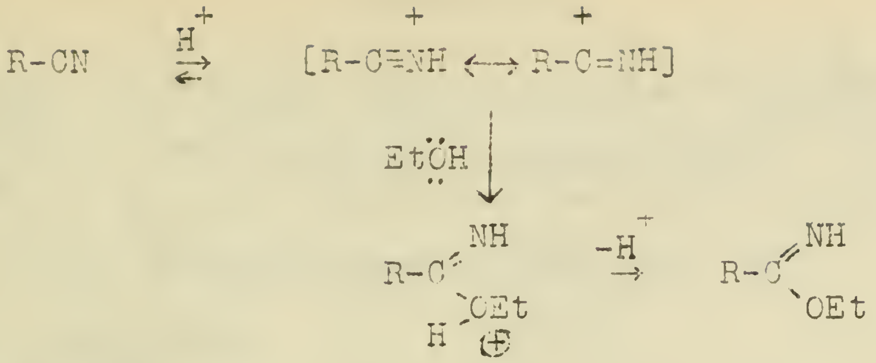
Additions to R-C≡N.--Since nitrogen, like oxygen, tends to attract shared electrons more strongly than carbon, it is reasonable to expect that the -C≡N group will show electrophilic properties similar to those of the -C=O group. However, this tendency should be weaker in the case of nitriles, since nitrogen lies to the left of oxygen in the periodic table, assuming, of course, that the difference between a double and a triple bond does not have an important effect.

1. Addition of Grignard Reagents.

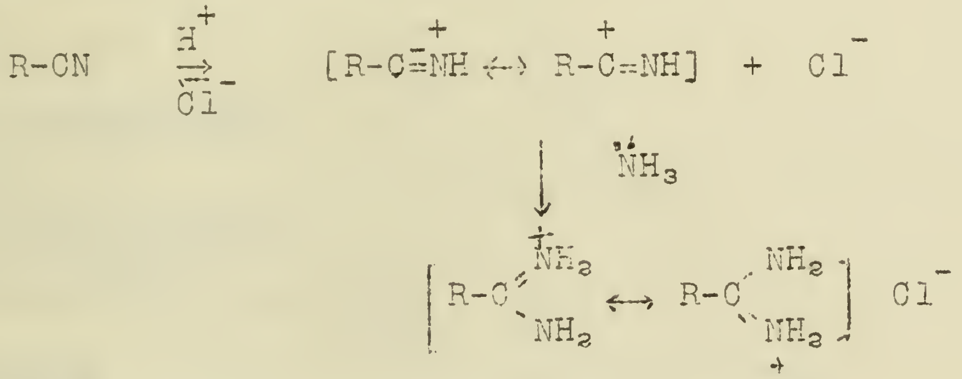
The reaction of nitriles with RMgX, with the carbanion $[:R^-]$ adding to the carbon atom, proceeds more slowly than similar additions to carbonyl compounds because of the relatively weak electropositive nature of the nitrile carbon.

2. Addition of Alcohols and Amines.

Alcohols, in the presence of acidic catalysts such as HCl, add to nitriles to form imino esters.

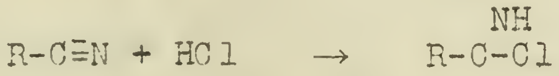


Amines, present as hydrochlorides or sulfonates, undergo the same type of acid-catalyzed addition to form amidine salts. In this case, the electron pair is supplied by the nitrogen atom; in the case of alcohols it was supplied by oxygen.



3. Addition of HX.

Although in acid media the oxygen atom in a carbonyl compound shows a decided tendency to add a hydrogen ion, stable adducts of strong acids of the HX type cannot be isolated. Such adducts, the imide halides, can be prepared and isolated in the case of nitriles, possibly because nitrogen is more basic (nucleophilic) than oxygen and has a greater affinity for strong acids.



$$R-C\equiv N + HCl \rightarrow R-\overset{NH}{C}-Cl$$

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Addition of Cyanide Ion
Hammett, p. 329.
Wheland, p. 244.

Hemiacetal Formation
Hammett, p. 303.

Mutarotation
Hammett, p. 337.

Addition of Hydroxylamine
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Addition of Semicarbazide
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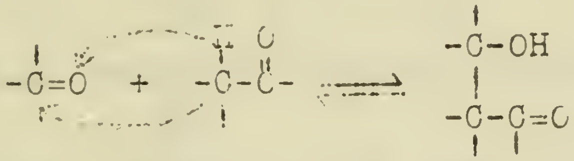
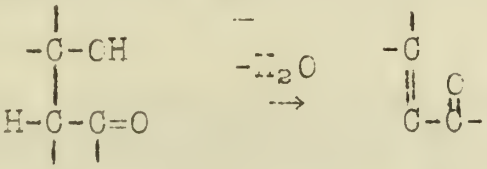
Remick, p. 125.
N. A. Higgins, Organic Seminar, 25, 27 (1947).

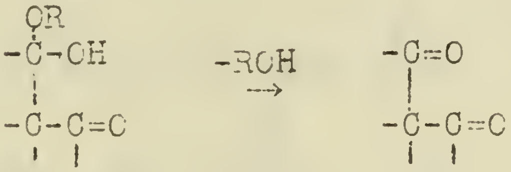
There are a number of reactions which are actually additions to a carbon-oxygen double bond, but which are somewhat disguised by the nature of the negative fragment which is involved. Thus all of the various condensation reactions which are known may be generalized as follows:



In some cases the initial reaction is followed by an elimination reaction (formation of α,β-unsaturated carbonyl compounds) or the hydrolysis of a hemiacetal of a β-keto carbonyl compound (Claisen Condensation).



(Perkin, Knoevenagel, Claisen-Schmidt)



(Claisen, Dieckmann)

Accordingly these reactions may be divided into three major groups:

I.- *Aldol Reactions* in which no subsequent elimination reaction occurs and which lead to β-hydroxy carbonyl compounds. (Aldol formation, Tollens condensation).

II.- *The Formation of α,β-Unsaturated Carbonyl Compounds* in which the initial addition reaction is followed by dehydration. (Perkin Reaction, Knoevenagel Condensation, Claisen-Schmidt Condensation).

III.- *Claisen Condensation* in which β-keto carbonyl compounds are formed by the hydrolysis of the hemiacetals which are formed initially. (Claisen Condensation, Dieckmann Condensation).

In addition to these types we shall discuss the reaction of *Grignard Reagents* with Carbonyl Compounds, the *Reformatsky Reaction* and the *Benzoin Condensation*. Although the first step of the *Mannich Reaction* probably proceeds by a similar path, we shall omit its consideration, since the exact nature of the latter stages of the reaction is not well understood.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

I. [illegible]

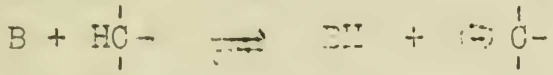
II. [illegible]

III. [illegible]

[illegible]

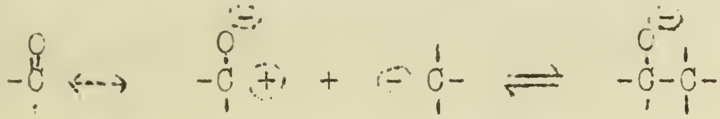
General Mechanism.

The Aldol reaction (as well as the initial steps of the formation of unsaturated carbonyl compounds and of the Claisen condensation) proceeds by the following generally accepted mechanism:

(1) 

$$B + H\overset{|}{\underset{|}{C}}- \rightleftharpoons BH + \ominus\overset{|}{\underset{|}{C}}-$$

(Base-catalyzed carbanion formation)

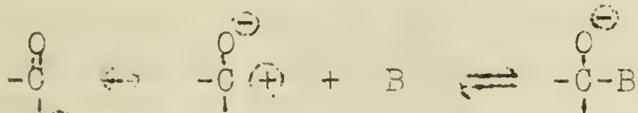
(2) 

$$-\overset{O}{\overset{\|}{\underset{|}{C}}} \longleftrightarrow -\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}\oplus + \ominus\overset{|}{\underset{|}{C}}- \rightleftharpoons -\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{|}{C}}-$$

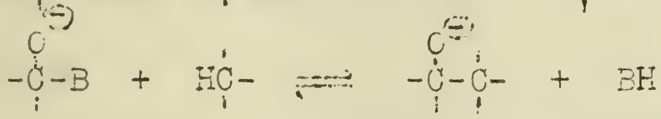
(Addition of the carbanion to the carbonyl carbon)

When catalyzed by acid, these reactions proceed by an altogether different mechanism, which will be considered in the next seminar.

Watson however favors a different mechanism on the basis of experiments in which the change of activation energies by substitutions in either of the reactants was studied.[1] This mechanism would consist in the initial addition of base to the carbonyl group (3), followed by a step such as (4):

(3) 

$$-\overset{O}{\overset{\|}{\underset{|}{C}}} \longleftrightarrow -\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}\oplus + B \rightleftharpoons -\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}-B$$

(4) 

$$-\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}-B + H\overset{|}{\underset{|}{C}}- \rightleftharpoons -\overset{O^{\ominus}}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{|}{C}}- + BH$$

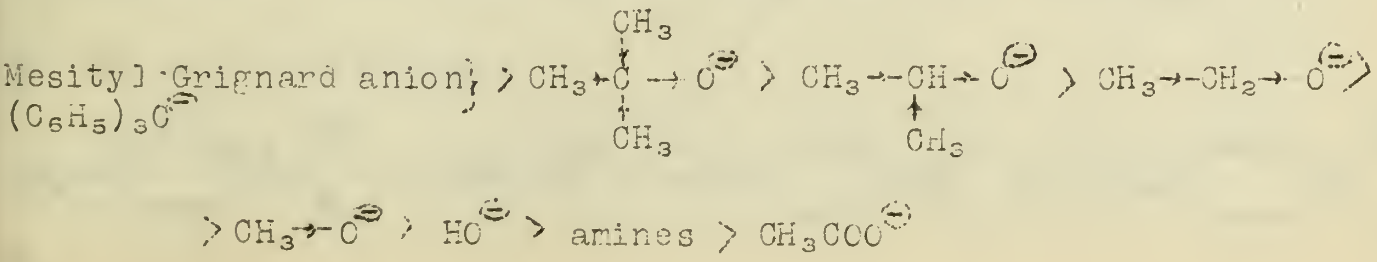
Since step (4) is no ordinary displacement reaction, most other workers prefer the former mechanism. Accordingly the following discussion will be developed from the point of view of equations (1) and (2).

Carbanion Formation

The ease of carbanion formation depends on external as well as internal (structural) factors.

External Factors.

The effectiveness of the catalyst increases with its basic strength:



Mesityl Grignard anion; $(C_6H_5)_3C^{\ominus}$ $> CH_3\rightarrow\overset{CH_3}{\overset{\downarrow}{\underset{\uparrow}{\underset{CH_3}{C}}}}\rightarrow O^{\ominus} > CH_3\rightarrow-\underset{\underset{CH_3}{\uparrow}}{CH}\rightarrow O^{\ominus} > CH_3\rightarrow-CH_2\rightarrow O^{\ominus} >$

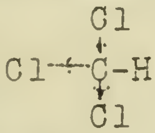
$> CH_3\rightarrow O^{\ominus} > HO^{\ominus} >$ amines $> CH_3COO^{\ominus}$

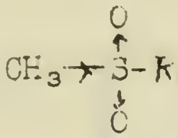
The less reactive the reactants, the stronger is the base that must be used.

Internal Factors.

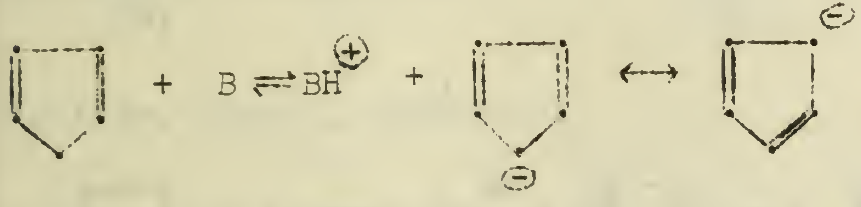
In general, carbanions will be formed only from compounds containing acidic hydrogens attached to carbon. Weakening of the C-H link may be due to structural influences in the unionized compound (I_s - effect), stabilization of the carbanion by resonance, or both:

I_s - effect only: Chloroform, Sulfones.





Resonance of Anion only: Cyclopentadiene, Indene, Fluorene.

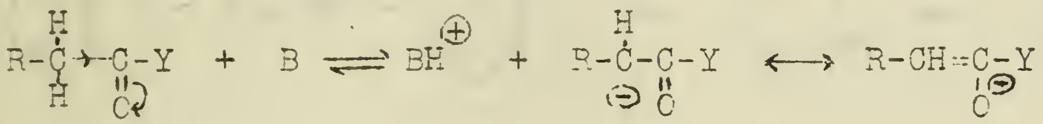


(and three more forms)

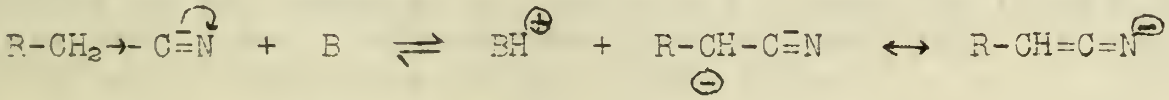
(Anion formation in indene and fluorene takes place somewhat less readily, because in some of the resonance forms the aromaticity of the benzene ring is destroyed).

Both Effects:

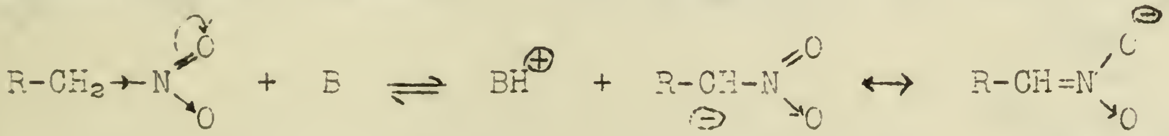
Aldehydes, Ketones, Acids, Esters, Anhydrides:



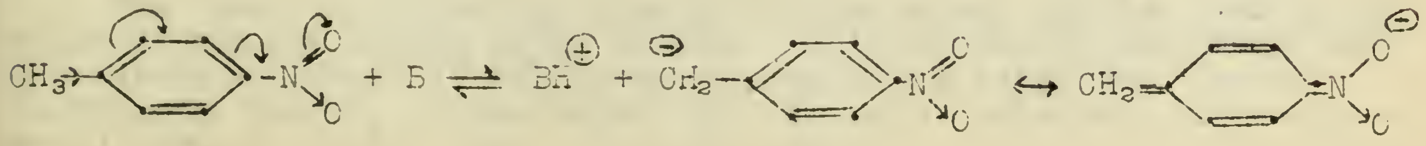
Nitriles:



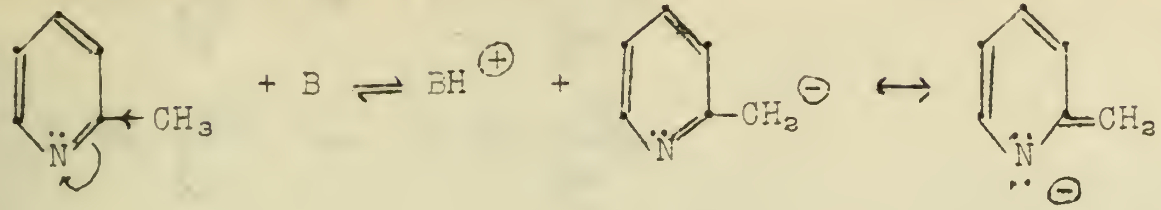
Aliphatic Nitro Compounds:



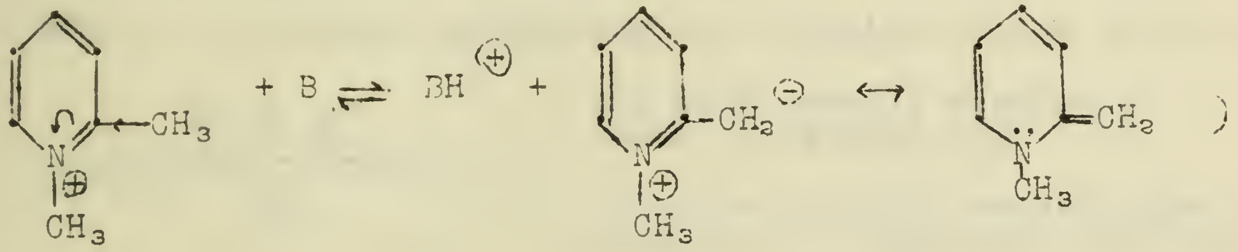
o- and p-nitrotoluenes:



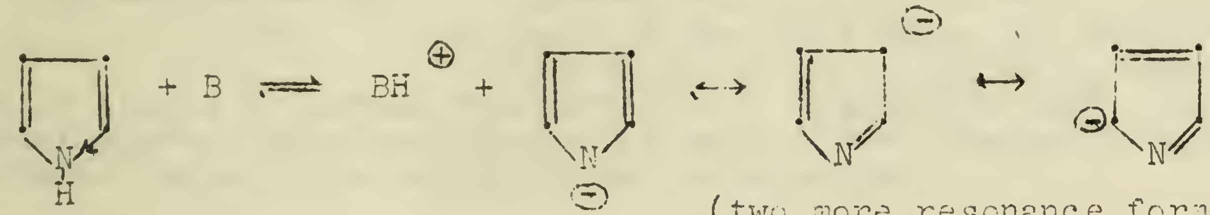
Picolines, Lutidines, Collidine; Quinaldine, Lepidine, etc.



(Picoline itself will not condense with benzaldehyde in the presence of piperidine, whereas picoline methiodide reacts readily. This is due to the powerful electron attraction of the unit positive charge:

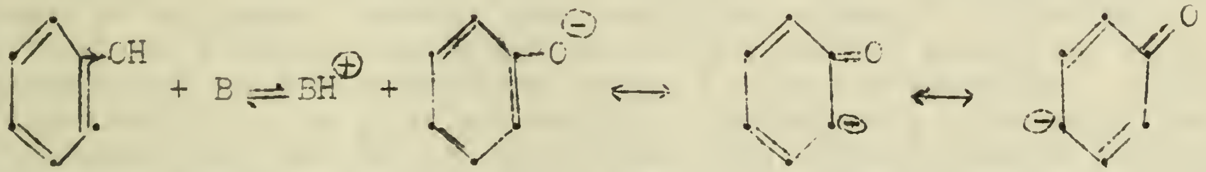


Pyrrole, Indole, Carbazole:

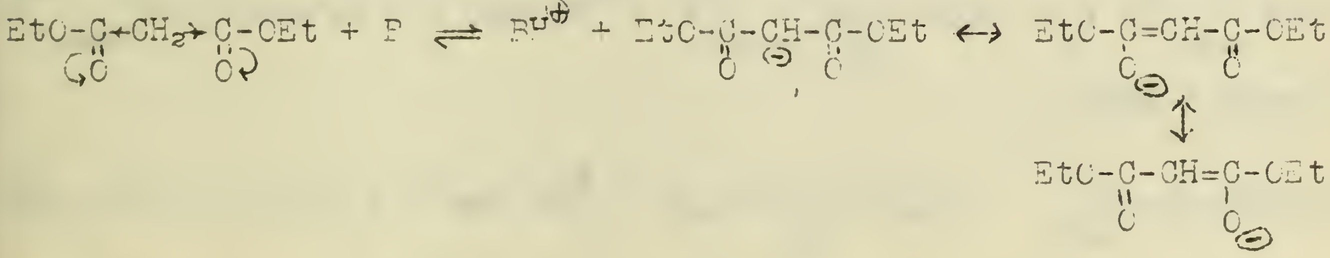


(two more resonance forms)

Phenols:



Carbanion formation is particularly easy when the C-H bond is weakened by two carbonyl or equivalent groups, as in malonic ester, cyanoacetic ester, β-ketoesters, β-diketones, etc. In these cases the carbanion resonates between three forms:

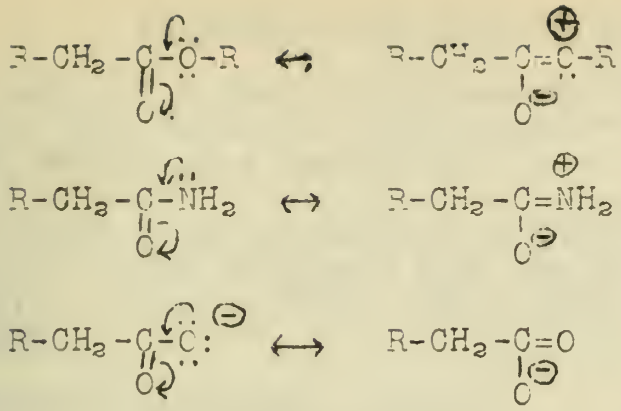


$$\mathrm{EtO{-}\underset{O}{\overset{}{C}}{\leftarrow}CH_2{\rightarrow}\underset{O}{C}{-}OEt + B \rightleftharpoons BH^{\oplus} + EtO{-}\underset{O}{C}{-}\underset{\ominus}{CH}{-}\underset{O}{C}{-}OEt \longleftrightarrow EtO{-}\underset{O^{\ominus}}{C}{=}CH{-}\underset{O}{C}{-}OEt}$$

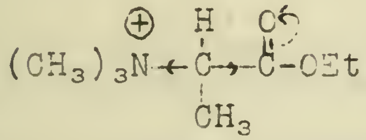
$$\updownarrow$$

$$\mathrm{EtO{-}\underset{O}{C}{-}CH{=}\underset{O^{\ominus}}{C}{-}OEt}$$

The ease of carbanion formation of ketones, esters, amides and acids decreases in the order listed. This is due to the fact that the electron demand of the carbonyl oxygen is satisfied, to an increasing degree, by the other atom (C or N) attached to the carbonyl carbon, rather than by the CH_2 group.



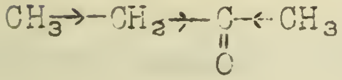
Effect of electron attracting or releasing groups in the molecule



$(CH_3)_3\overset{\oplus}{N}\leftarrow\underset{CH_3}{\overset{H}{C}}\rightarrow\overset{O}{\overset{\|}{C}}-OEt$

C-H bond greatly weakened. (Rapid racemization)

(Compare also the reactivities of picoline and picoline methiodide)

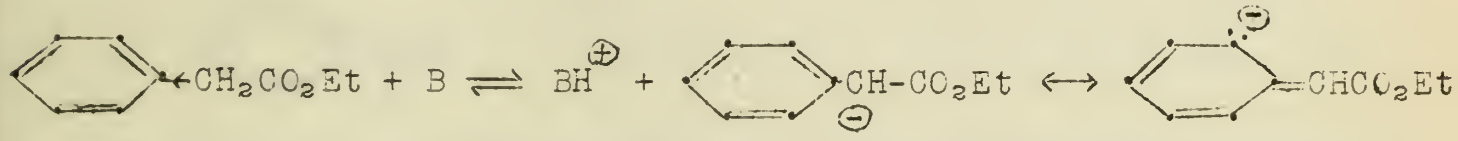


$CH_3\rightarrow-CH_2\rightarrow-\underset{O}{\underset{\|}{C}}\leftarrow CH_3$

Electron release (I_D-effect) of the methyl group on the left makes the methylene group less prone to lose a proton. Thus one should expect to obtain the carbanion: $CH_3-CH_2-CO-CH_2^{\ominus}$. In fact benzaldehyde, isobutyraldehyde and some other α-branched aldehydes condense through the methyl group, as expected.

However, formaldehyde and straight chain aliphatic aldehydes appear to condense through the methylene group.[2] This may be due to the fact that while condensation on the methyl group is more rapid, condensation on the methylene group is less reversible. Electronic shifts permit us to predict reaction rates only--the position of the equilibrium may not be in accordance with the rates of reaction. (Cf. dissociation constants and rate of neutralization of nitroparaffins.)

Phenyl and Vinyl groups facilitate carbanion formation:



(and 2 more)

$$CH_2=CH\leftarrow CH_2CO_2Et + B \rightleftharpoons BH^{\oplus} + CH_2=CH-\underset{\ominus}{CH}-CO_2Et \qquad \underset{\ominus}{CH_2}-CH=CHCO_2Et$$

(These resonance forms are additional to the usual ones of the enolate ions mentioned above.)

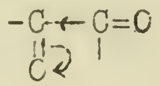
Structural Influences on the Carbonyl Group

Any group that withdraws electrons from the carbonyl group favors base-catalyzed condensation reactions by rendering the carbonyl carbon more positive.

Conversely any source of electrons will render condensation more difficult by permitting the oxygen to acquire a fractional negative charge without the carbon acquiring an equivalent positive charge.

Electron-withdrawing groups:

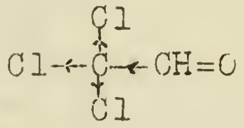
(a) α-Carbonyl:



$-\underset{O}{\underset{\|}{C}}\leftarrow \underset{|}{C}=O$

This explains the superior reactivity of oxalic ester in crossed Claisen condensations.

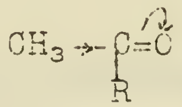
(b) α-Chloroaldehydes and -ketones:



$Cl\leftarrow \overset{Cl}{\underset{Cl}{C}}\leftarrow CH=O$

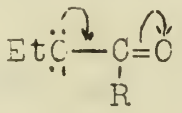
Electron-releasing groups:

(a) Ketones are less reactive than aldehydes:



$CH_3\rightarrow \underset{R}{C}=O$

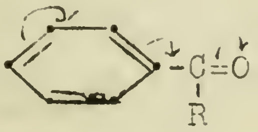
(b) Esters, etc., are less reactive than ketones:



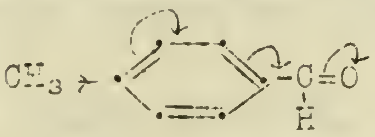
$Et\ddot{O}-\underset{R}{C}=O$

(Compare the use of the strong base $NH_2^{\ominus}$ in the condensation of ethyl acetate with acetone with the use of the weaker base OH^{-} (Barium hydroxide) in the self-condensation of acetone.)

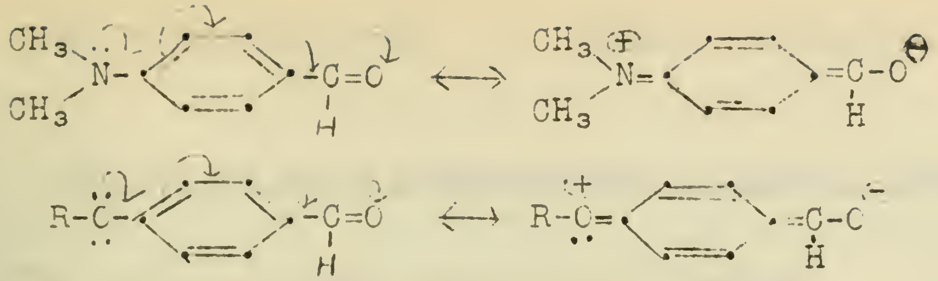
(c) Aryl groups.



The effect of substituents in the benzene ring has been studied in connection with the Perkin reaction. Methyl groups decrease the rate and yield, presumably by hyperconjugation.

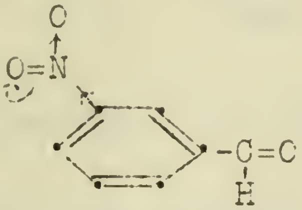


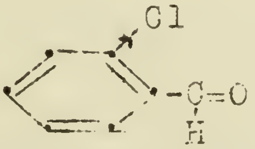
p-Dimethylaminobenzaldehyde and p-alkoxybenzaldehydes are also very unreactive:



A methoxy group in the ortho position, however, actually enhances the reactivity. The explanation of this anomaly is not well understood.

A halogen or nitro group in any position increases the rate and the yield, by reducing the electron-releasing effect of the ring:

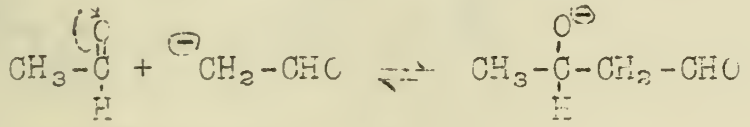




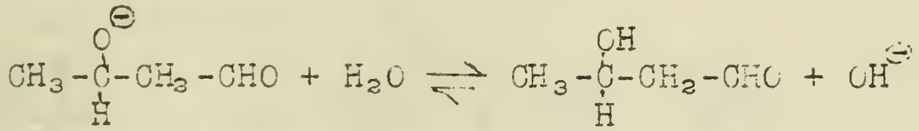
Aldol Reactions

These reactions proceed between simple aliphatic aldehydes and ketones in the presence of an inorganic base:

(1) $CH_3-CH=O + OH^{\ominus} \rightleftharpoons H_2O + {}^{\ominus}CH_2-CH=O \longleftrightarrow CH_2=CH-O^{\ominus}$

(2) 

$$CH_3-\overset{O}{\underset{H}{C}} + {}^{\ominus}CH_2-CHO \rightleftharpoons CH_3-\overset{O^{\ominus}}{\underset{H}{C}}-CH_2-CHO$$

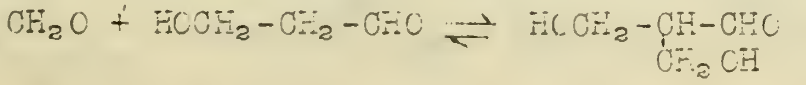
(3) 

$$CH_3-\overset{O^{\ominus}}{\underset{H}{C}}-CH_2-CHO + H_2O \rightleftharpoons CH_3-\overset{OH}{\underset{H}{C}}-CH_2-CHO + OH^{\ominus}$$

In the case of aldehydes, step (1) is rate determining, as proved by the failure of deuterium to become attached to carbon if the reaction is run in D_2O. With ketones, on the other hand, step (2) is rate determining.

A special Aldol reaction is the Tollens condensation (formaldehyde with other aldehydes or ketones in the presence of lime water). The high reactivity of formaldehyde, which is due to the absence of electron-releasing alkyl groups, may lead to the formation of polymethylol derivatives.

$CH_2O + CH_3CHO \rightleftharpoons HOCH_2-CH_2-CHO$



$$CH_2O + HOCH_2-CH_2-CHO \rightleftharpoons HOCH_2-\underset{CH_2OH}{CH}-CHO$$

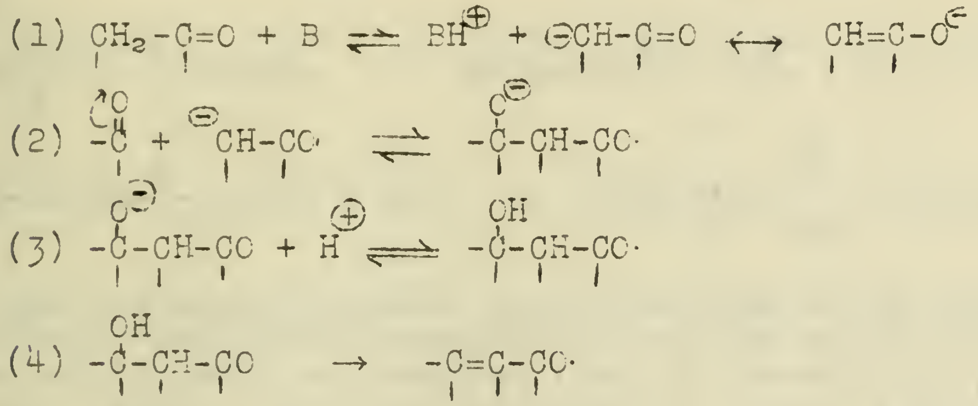
$CH_2O + (HOCH_2)_2CH-CHO \rightleftharpoons (HOCH_2)_3C-CHO$

} Aldol reactions

$CH_2O + (HOCH_2)_3C-CHO \rightarrow HCO_2H + C(CH_2OH)_4$ (Crossed Cannizzaro)

Formation of α,β-Unsaturated Carbonyl Compounds

The general mechanism is the following:



$$(1)\; CH_2-C=O + B \rightleftharpoons BH^{\oplus} + {}^{\ominus}CH-C=O \longleftrightarrow CH=C-O^{\ominus}$$

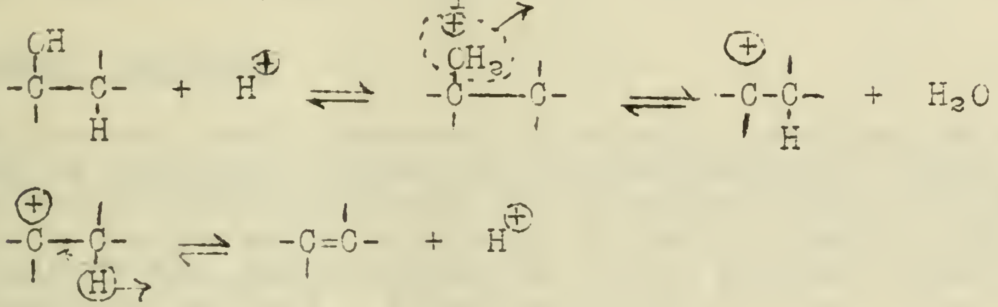
$$(2)\; -\overset{O}{\overset{\|}{C}} + {}^{\ominus}CH-CO \rightleftharpoons -\overset{O^{\ominus}}{C}-CH-CO$$

$$(3)\; -\overset{O^{\ominus}}{C}-CH-CO + H^{\oplus} \rightleftharpoons -\overset{OH}{C}-CH-CO$$

$$(4)\; -\overset{OH}{C}-CH-CO \rightarrow -C=C-CO$$

Step (4) can proceed by acid or by base catalysis:

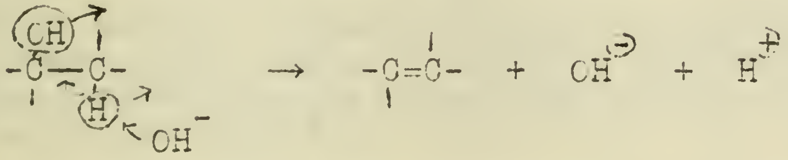
(a) Acid catalysis: (E_1)



$$-\overset{OH}{C}-\underset{H}{C}- + H^{\oplus} \rightleftharpoons -\overset{\overset{\oplus}{OH_2}}{C}-C- \rightleftharpoons -\overset{\oplus}{C}-\underset{H}{C}- + H_2O$$

$$-\overset{\oplus}{C}-\underset{H}{C}- \rightleftharpoons -C=C- + H^{\oplus}$$

(b) Base catalysis: (E_2)

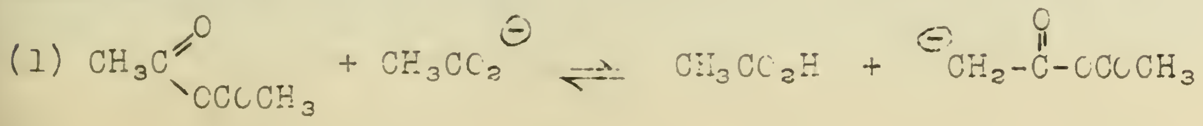


$$-\overset{OH}{C}-\underset{H}{C}- \;\; OH^- \rightarrow -C=C- + OH^{\ominus} + H^{\oplus}$$

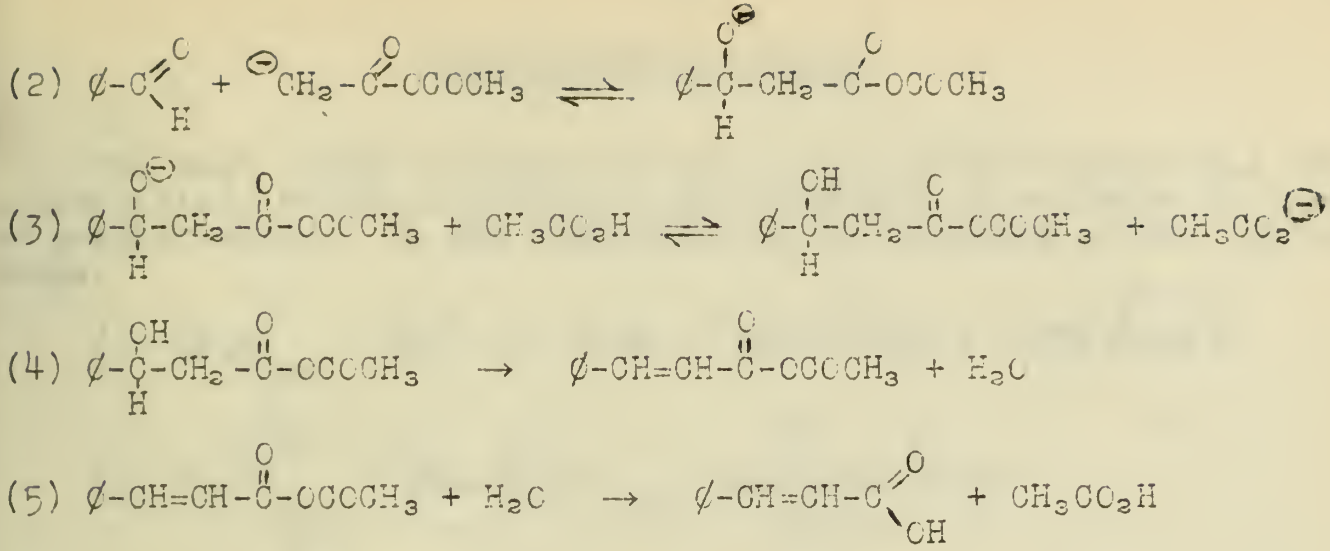
Whether the fourth step be acid or base catalyzed, step (3) must occur first, before water can be eliminated. Thus in any event an acid catalyst must be present, in addition to the base catalyst required for the carbanion formation.[3]

Perkin reaction[4]

Mechanism:



$$(1)\; CH_3C\begin{matrix}\nearrow O\\ \searrow OCOCH_3\end{matrix} + CH_3CO_2^{\ominus} \rightleftharpoons CH_3CO_2H + {}^{\ominus}CH_2-\overset{O}{\overset{\|}{C}}-OCOCH_3$$



(2) $\phi\text{-}C{\overset{O}{\underset{H}{}}} + {}^{\ominus}CH_2\text{-}\overset{O}{C}\text{-}OCOCH_3 \rightleftharpoons \phi\text{-}\underset{H}{\overset{O^{\ominus}}{C}}\text{-}CH_2\text{-}\overset{O}{C}\text{-}OCOCH_3$

(3) $\phi\text{-}\underset{H}{\overset{O^{\ominus}}{C}}\text{-}CH_2\text{-}\overset{O}{C}\text{-}OCOCH_3 + CH_3CO_2H \rightleftharpoons \phi\text{-}\underset{H}{\overset{OH}{C}}\text{-}CH_2\text{-}\overset{O}{C}\text{-}OCOCH_3 + CH_3CO_2^{\ominus}$

(4) $\phi\text{-}\underset{H}{\overset{OH}{C}}\text{-}CH_2\text{-}\overset{O}{C}\text{-}OCOCH_3 \rightarrow \phi\text{-}CH{=}CH\text{-}\overset{O}{C}\text{-}OCOCH_3 + H_2O$

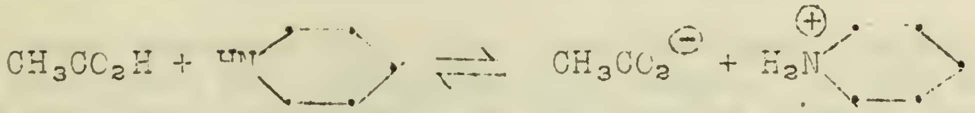
(5) $\phi\text{-}CH{=}CH\text{-}\overset{O}{C}\text{-}OCOCH_3 + H_2O \rightarrow \phi\text{-}CH{=}CH\text{-}C{\overset{O}{\underset{OH}{}}} + CH_3CO_2H$

The following evidence indicates that it is actually the anhydride that forms the carbanion and not the salt: (a) If the anhydride and the salt are derived from different acids, the yields of the two possible condensation products parallel the amounts of the anhydrides present in the equilibrium mixture of the salt-anhydride at the temperature of the reaction. (b) We can use an alkali carbonate or an organic base instead of the salt of an organic acid.[5]

Knoevenagel reaction

As we have seen, presence of an acid catalyst in addition to the base is essential; thus pure benzaldehyde will not condense with malonic ester in the presence of piperidine, but will condense readily in the presence of traces of benzoic acid. Superior yields are obtained when the reaction is run in glacial acetic acid; amine salts may also be used. If malonic acid is one of the reactants, no additional acid is of course required.

If we use for instance piperidine acetate, either piperidine or the acetate ion may be considered as the base which catalyzes carbanion formation; the piperidonium ion or acetic acid functions as the acid catalyst.[6]



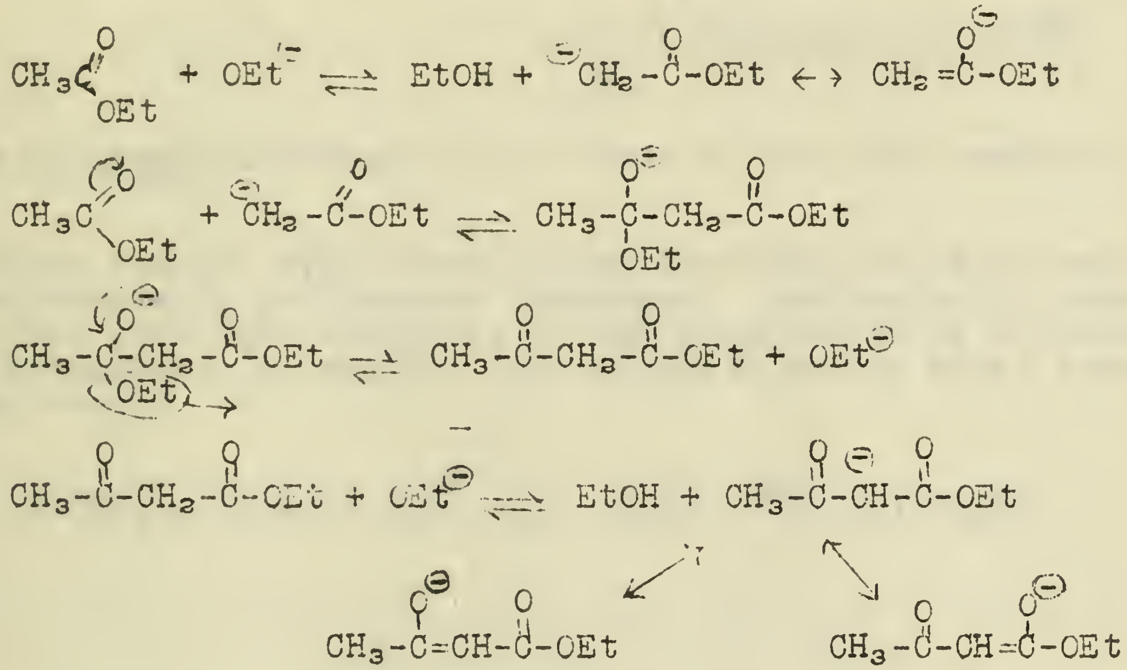
$CH_3CO_2H + HN\langle\ \rangle \rightleftharpoons CH_3CO_2^{\ominus} + H_2\overset{\oplus}{N}\langle\ \rangle$

Claisen-Schmidt reaction

This reaction, which is characterized by the use of 10% aqueous NaOH, is used generally for the condensation of aromatic aldehydes with ketones. Dehydration takes place readily owing to the electron mobility in the ring.

Claisen Condensations[7]

The most common reaction of this type is the acetoacetic ester condensation, which consists in the acylation of an ester by itself or another ester. In the simplest case it consists of the following steps:



$$(1)\quad CH_3C\overset{O}{\underset{OEt}{\lessdot}} + OEt^- \rightleftharpoons EtOH + {}^{\ominus}CH_2-\overset{O}{\overset{\|}{C}}-OEt \leftrightarrow CH_2=\overset{O^{\ominus}}{\overset{|}{C}}-OEt$$

$$(2)\quad CH_3C\overset{O}{\underset{OEt}{\lessdot}} + {}^{\ominus}CH_2-\overset{O}{\overset{\|}{C}}-OEt \rightleftharpoons CH_3-\overset{O^{\ominus}}{\overset{|}{\underset{OEt}{\underset{|}{C}}}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt$$

$$(3)\quad CH_3-\overset{O^{\ominus}}{\overset{|}{\underset{OEt}{\underset{|}{C}}}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt \rightleftharpoons CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt + OEt^{\ominus}$$

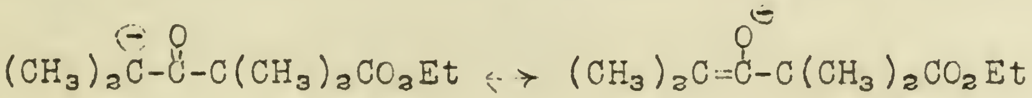
$$(4)\quad CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt + OEt^{\ominus} \rightleftharpoons EtOH + CH_3-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-OEt$$

$$CH_3-\overset{O^{\ominus}}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OEt \qquad CH_3-\overset{O}{\overset{\|}{C}}-CH=\overset{O^{\ominus}}{\overset{|}{C}}-OEt$$

In general, Claisen condensations will proceed when a base is formed that is weaker than the condensing agent. Thus in the formation of acetoacetic ester, the ion formed in the last step is a weaker base than the ethoxide ion, as it is stabilized by the presence of three different resonance forms.

Formation of such an anion with more than two resonance forms is possible only in the condensation of esters having at least two hydrogens _α_ to the carbethoxy group. Thus ethyl isobutyrate cannot undergo self-condensation or condensation with ethyl benzoate in the presence of sodium ethoxide, as none of the ions formed in the reaction is a weaker base (more stable ion) than ethoxide ion itself.

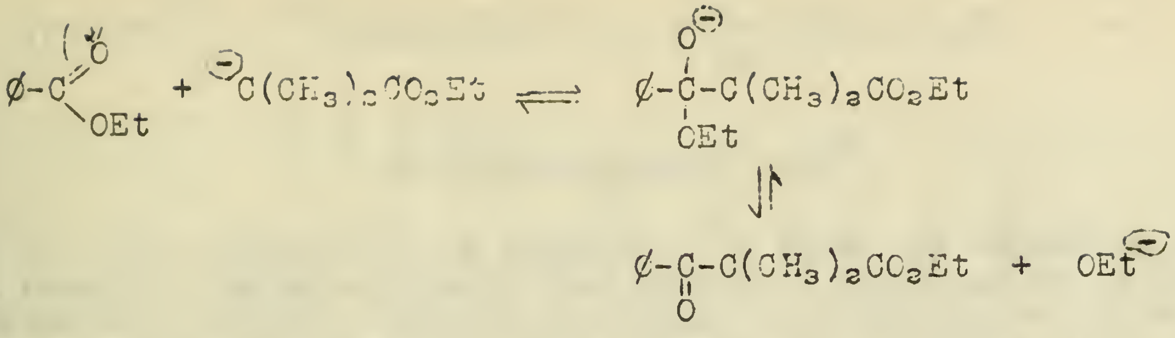
Hauser found however that these condensations proceed satisfactorily when catalyzed by triphenylmethyl sodium. In the self-condensation of ethyl isobutyrate an enolate is formed which, though not a weaker base than ethoxide is weaker than $\phi_3C^{\ominus}$:[8]



$$(CH_3)_2\overset{\ominus}{C}-\overset{O}{\overset{\|}{C}}-C(CH_3)_2CO_2Et \leftrightarrow (CH_3)_2C=\overset{O^{\ominus}}{\overset{|}{C}}-C(CH_3)_2CO_2Et$$

In the condensation of ethyl isobutyrate with ethyl benzoate, the end product cannot enolize at all; still, the reaction proceeds, because ϕ_3C^- is a stronger base than the OEt^- ion formed:[9]

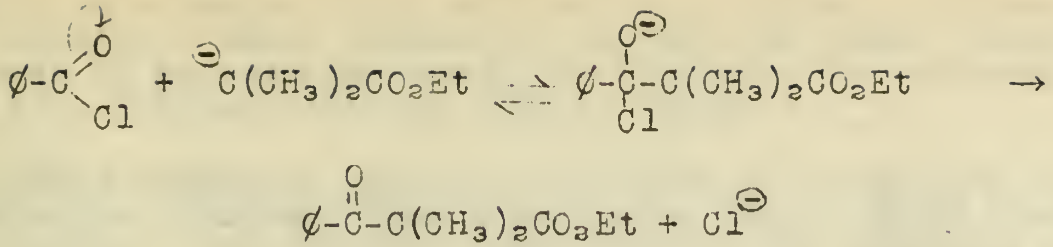
$$H\dot{C}(CH_3)_2CO_2Et + \phi_3C^{\ominus} \rightleftharpoons \phi_3CH + {}^{\ominus}C(CH_3)_2CO_2Et$$



The Dieckmann condensation proceeds by the same mechanism.

Another Claisen type reaction involves the use of an acid chloride or anhydride in β-ketoester syntheses. Particularly good yields are obtained with acid chlorides in the preparation of α,α-disubstituted β-ketoesters, as the Cl⁻ ion liberated in the final step is a very weak base:

$$(1)\ HC(CH_3)_2\text{-}CO_2Et + \phi_3C^{\ominus} \rightleftharpoons \phi_3CH + {}^{\ominus}C(CH_3)_2CO_2Et$$

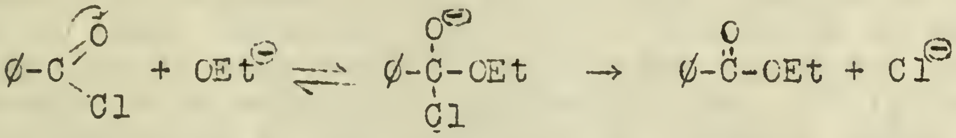
(2) 

$$\phi\text{-}C\overset{O}{\underset{Cl}{\diagup\!\!\diagdown}} + {}^{\ominus}C(CH_3)_2CO_2Et \rightleftharpoons \phi\text{-}\underset{Cl}{\overset{O^{\ominus}}{C}}\text{-}C(CH_3)_2CO_2Et \rightarrow \phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}C(CH_3)_2CO_2Et + Cl^{\ominus}$$

With an acid chloride it is essential to form the carbanion first, by a reaction going to completion (which is the case if we use triphenylmethyl sodium), because otherwise a competing reaction takes place in which the base catalyst adds to the carbonyl group with subsequent elimination of Cl^-.[10]

Thus if we use sodium ethoxide, the equilibrium in reaction (1) lies largely to the left and the overall result is replacement of Cl^- by OEt^-:

$$(1)\ HC(CH_3)_2CO_2Et + OEt^{-} \rightleftharpoons {}^{\ominus}C(CH_3)_2CO_2Et + EtOH$$

(1-a) 

$$\phi\text{-}C\overset{O}{\underset{Cl}{\diagup\!\!\diagdown}} + OEt^{\ominus} \rightleftharpoons \phi\text{-}\underset{Cl}{\overset{O^{\ominus}}{C}}\text{-}OEt \rightarrow \phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}OEt + Cl^{\ominus}$$

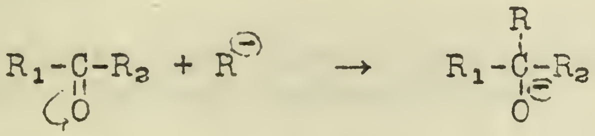
The Claisen type condensations also include the acylation of methyl ketones, in which case sodamide is the best catalyst.[11] This reaction proceeds by essentially the same mechanism.

Grignard and Reformatsky Reactions

The Grignard reagent may be supposed to dissociate into both ions and free radicals:

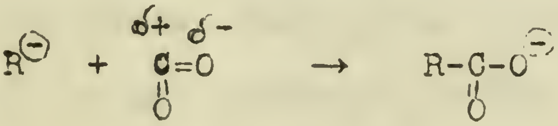
$$R^{\bullet} + {}^{\bullet}MgX \rightleftharpoons R\text{-}MgX \rightleftharpoons R^{\ominus} + MgX^{\oplus}$$

In the presence of a strongly polar group, such as a carbonyl group, one would expect the reagent to react in the ionic form:



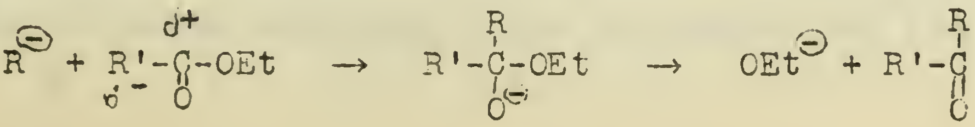
$$R_1\text{-}\underset{O}{\underset{\|}{C}}\text{-}R_2 + R^{\ominus} \rightarrow R_1\text{-}\underset{O^{\ominus}}{\overset{R}{C}}\text{-}R_2$$

The formation of acids is explained thus:



$$R^{\ominus} + \underset{O}{\underset{\|}{\overset{\delta+}{C}}}=\overset{\delta-}{O} \rightarrow R\text{-}\underset{O}{\underset{\|}{C}}\text{-}O^{-}$$

In the reaction with esters, an alkoxide anion is eliminated in a fashion similar to that in the Claisen condensation:

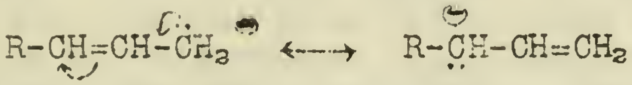


$$R^{\ominus} + R'\text{-}\overset{\delta+}{\underset{\delta-\ O}{C}}\text{-}OEt \rightarrow R'\text{-}\underset{O^{\ominus}}{\overset{R}{C}}\text{-}OEt \rightarrow OEt^{\ominus} + R'\text{-}\underset{O}{\underset{\|}{\overset{R}{C}}}$$

The product is a ketone which will undergo further reaction with the Grignard reagent. Small amounts of ketones (or their pinacols in the presence of excess magnesium) may sometimes be isolated from the reaction of a Grignard reagent with an ester.

The above mechanism explains the order of reactivity of carbonyl compounds towards Grignard reagents, viz.: R-CHO > R-CO-R > R-CO-Ar > RCCOEt. The relative reactivity of the Grignard reagents, on the other hand, is not so readily explained, since steric factors seem to play an important part here. Steric factors also seem to be predominantly responsible for abnormal reactions with highly branched compounds (Reduction, enolate formation and coupling).

On the other hand, the allylic shifts sometimes observed in the reactions of certain Grignard reagents, like crotyl magnesium bromide, are readily explained by the resonance of the carbanion:



$$R-CH=CH-\overset{\ominus}{\ddot{C}H_2} \longleftrightarrow R-\underset{\cdot\cdot}{\overset{\ominus}{C}}H-CH=CH_2$$

Organo-zinc compounds are essentially similar to organo-magnesium compounds in their behavior, but their reactivity is somewhat diminished. Thus while they readily react with aldehydes and ketones, their reaction with esters is extremely slow. It is for this reason that the preparation of the organo-zinc compound which serves as an intermediate in the Reformatsky reaction from a bromo ester is possible.

Benzoin Condensation

The benzoin condensation is specifically catalyzed by cyanide ion, although benzoin condensations have been brought about by means of equivalent amounts of Mg or amalgamated Al.[12] This latter type of condensation seems to proceed by a free radical mechanism (ketyl formation, similar to acyloin condensations and pinacol formation, as discussed in the previous seminar).

A mechanism for the benzoin condensation should explain the following facts:

(1) Aldehydes that have α-hydrogens undergo an aldol rather than a benzoin condensation.

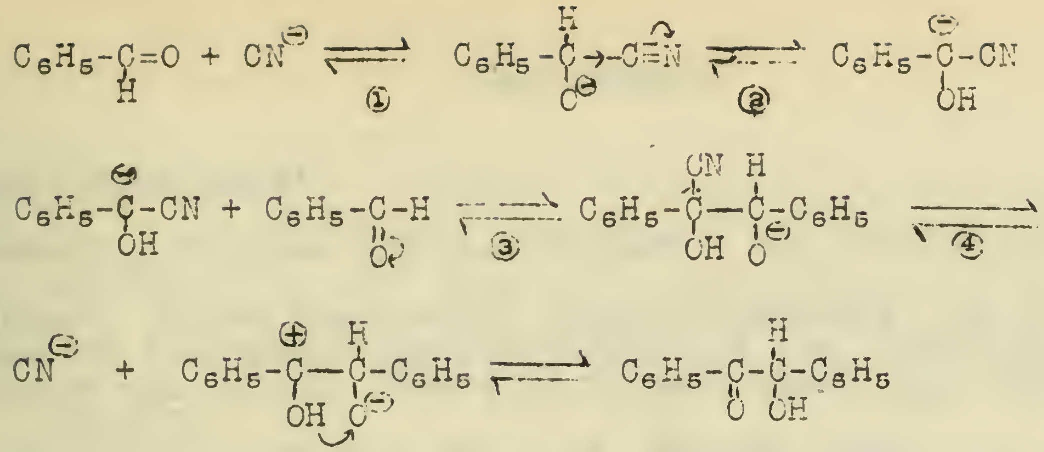
(2) The benzoin condensation is reversible.[13-15]

(3) It follows third order kinetics: $v = k[RCHO]^2[CN^-]$.[16,17]

(4) It is not catalyzed by HCN or complex cyanides.

(5) Increase in the alkalinity of the medium does not increase the rate of benzoin formation.

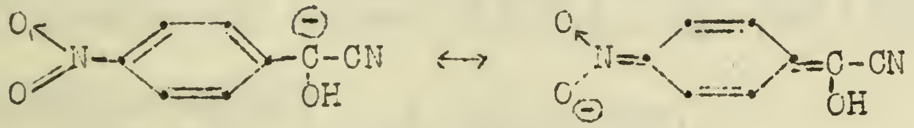
The following mechanism seems to account for all the facts:



Third order kinetics demands that step 3 or 4 be rate determining. In an alkali cyanide medium, the cyanchydrin anion concentration is sufficiently high so that further increase in the alkalinity does not augment the reaction rate (step 3 and 4 still determine the rate). However, in an acid medium (e.g. HCN), the cyanohydrin anion is largely converted into the cyanohydrin. Consequently Step (2) becomes very slow and the reaction does not proceed.

The cyanide ion is specific, because its tendency to withdraw electrons makes possible the proton shift (2).

Substituents in the benzene ring usually slow down the benzoin condensation and in many cases [p-OH, $-NO_2$, p-$N(CH_3)_2$, halogens] suppress it altogether.[18] The explanation seems to be that a substituent with a -I or -M effect, as a nitro group, makes the cyanohydrin anion unreactive:

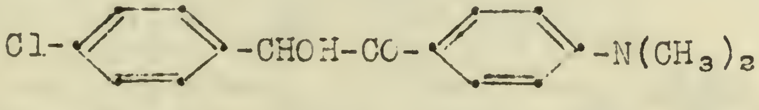


(Type I)

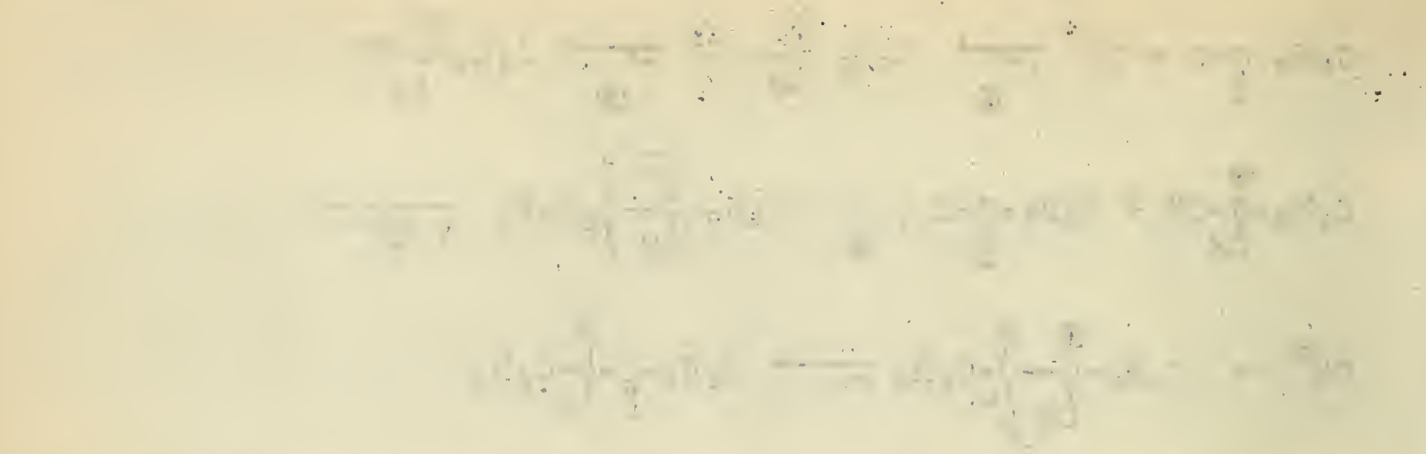
while a substituent with a +I or +M effect, like a dimethylamino group, will prevent the aldehyde molecule from condensing with the (reactive) cyanohydrin anion (cf. page 7) (Type II).

The above interpretation makes it plausible that unreactive aldehydes, while not condensing with themselves, might undergo mixed benzoin condensations with benzaldehyde or with aldehydes of the opposite type. This is borne out by experiment (except in the case of nitrobenzaldehydes which do not seem to form benzoins of any kind). As expected by the mechanism, since the type II aldehyde supplies the reactive cyanohydrin anion, it will also supply the carbonyl group of the benzoin.[19-21]

Example:



The equilibrium between two mixed benzoins: $R\text{-}CHOH\text{-}CO\text{-}R' \rightleftharpoons R\text{-}CO\text{-}CHOH\text{-}R'$ can be established not only by heating with KCN but also by heat alone.[22,23] The experimental equilibrium constant agrees with the value calculated from the redox potentials of the aldehydes involved.[2] In the above instances, the equilibrium is so far shifted to one side that only one mixed benzoin can be isolated.

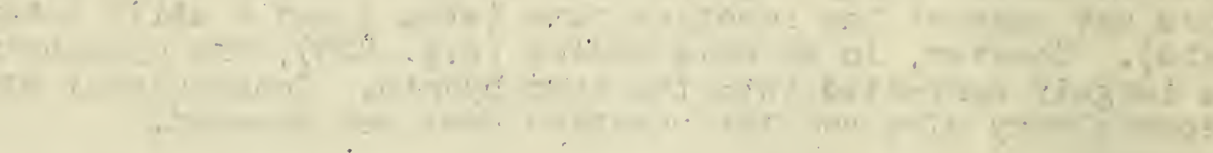


Third order kinetics [illegible] intermedi-ate. [illegible]

[illegible]

The reaction can be explained, however, [illegible] electrophilic [illegible] (IV).

[illegible]



(type I)

[illegible]

[illegible]

Example:

[illegible]

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Carbanion Formation
(2) Powell, J. A. C. S., 46, 2514 (1924); 55, 1153 (1933); 58, 1871 (1936).

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(3) Breslow and Hauser, J.A.C.S., 61, 793 (1939).

Perkin Reaction
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Knoevenagel Reaction
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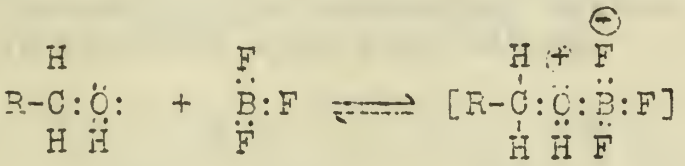
Introduction.

According to the Lewis concept of acids and bases, an acid is any substance which is capable of accepting a share in a pair of electrons from another substance to form a coordinate-covalent bond. The acid catalysts are composed such as P_2O_5, SO_3, halides of Boron, Aluminum, Tin, Iron, and Zinc, as well as the hydrogen acids HF, HCl, H_3PO_4, and H_2SO_4. Their catalytic activity stems from their ability to affiliate themselves with the unshared electrons of another compound.

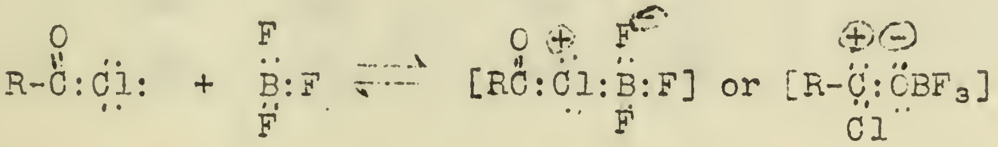
The steps in an acid-catalyzed reaction are quite general and may be summarized as follows:

1. The acid forms a coordinate-covalent bond with one of the reacting substances. Usually the bond utilizes an already existing pair of unshared electrons, but in the case of unsaturated compounds the double bond may be utilized leaving an electron deficient carbon and consequently a positively charged complex molecule.



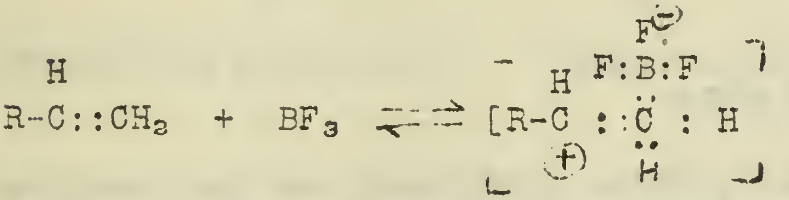
$$R\text{-}\underset{H}{\overset{H}{C}}:\underset{H}{\ddot{O}}: + \underset{F}{\overset{F}{\ddot{B}}}:F \rightleftharpoons [R\text{-}\underset{H}{\overset{H}{C}}:\underset{H}{\overset{\oplus}{\ddot{O}}}:\underset{F}{\overset{F^{\ominus}}{\ddot{B}}}:F]$$

(1)



$$R\text{-}\overset{O}{C}:\ddot{Cl}: + \underset{F}{\overset{F}{\ddot{B}}}:F \rightleftharpoons [R\overset{O}{C}:\overset{\oplus}{Cl}:\underset{F}{\overset{F^{\ominus}}{\ddot{B}}}:F] \text{ or } [R\text{-}\underset{Cl}{\overset{\oplus}{C}}:\overset{\ominus}{C}BF_3]$$

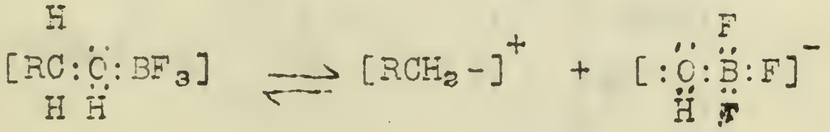
(2)



$$R\text{-}\overset{H}{C}::CH_2 + BF_3 \rightleftharpoons \left[R\text{-}\underset{\oplus}{\overset{H}{C}}::\underset{H}{\overset{F:\overset{F^{\ominus}}{B}:F}{\ddot{C}}}:H\right]^{-}$$

(3)

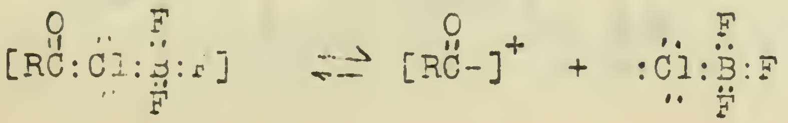
2. In the instances where the complex molecule is uncharged, an ionization then occurs. This results in the formation of a "Carbonium ion." This may be either an "alkyl" or an "acyl" fragment, depending on the type of complex molecule involved. Alkyl Halides, Alcohols, and Ethers produce alkyl fragments.



$$[R\underset{H}{\overset{H}{C}}:\underset{H}{\ddot{O}}:BF_3] \rightleftharpoons [RCH_2-]^{+} + [:\underset{H}{\ddot{O}}:\underset{F}{\overset{F}{\ddot{B}}}:F]^{-}$$

(4)

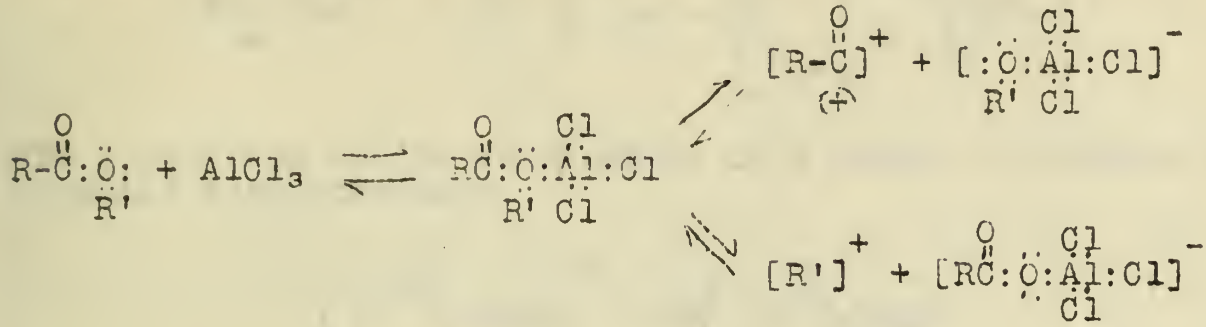
Carboxy compounds, Acyl Halides, and Carboxy anhydrides produce complexes which ionize to acyl fragments.



$$[R\overset{O}{C}:\ddot{Cl}:\underset{F}{\overset{F}{\ddot{B}}}:F] \rightleftharpoons [R\overset{O}{C}-]^{+} + :\ddot{Cl}:\underset{F}{\overset{F}{\ddot{B}}}:F$$

(5)

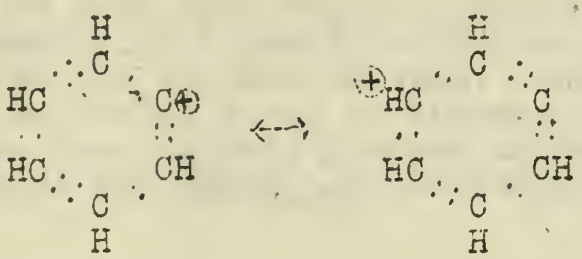
Esters may result in either alkyl or acyl carbonium ions depending upon the relative stability of the two possibilities.



(6a)

(6b)

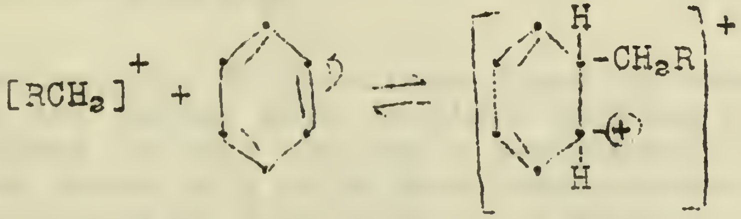
Esters of aliphatic compounds produce alkyl fragments (b). Esters of aromatic compounds produce acyl fragments (a). This follows from the fact that inasmuch as the acyl group is more electrophilic than the alkyl group, it will not ordinarily be released. However, in the case of an aromatic substituent, the requisite phenyl carbonium ion is incapable of maintaining the necessary resonance for stability since any shift of electrons would destroy the conjugated resonating system. Accordingly, the acyl radical is released from such esters.



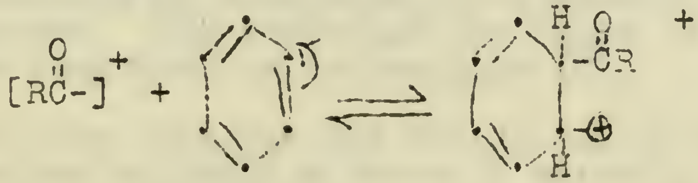
(7)

(Phenyl Carbonium Ion) (Slight contribution towards stabilization)

3. The carbonium ions are themselves acidic, according to the Lewis view, and have a great tendency to accept a share in still other electron pairs. The positively charged complexes derived from olefins, although not further "ionized," are also capable of sharing electron pairs.



(8)



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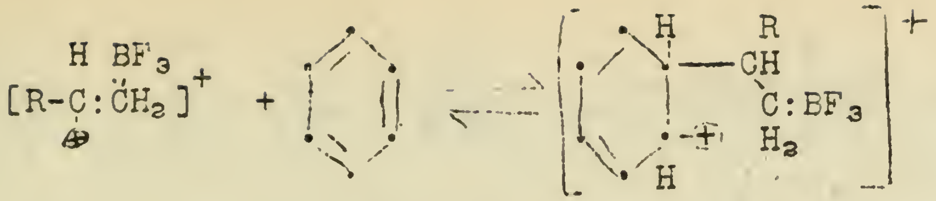
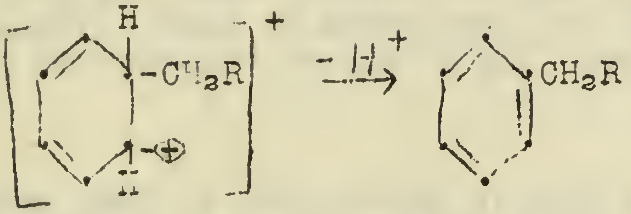
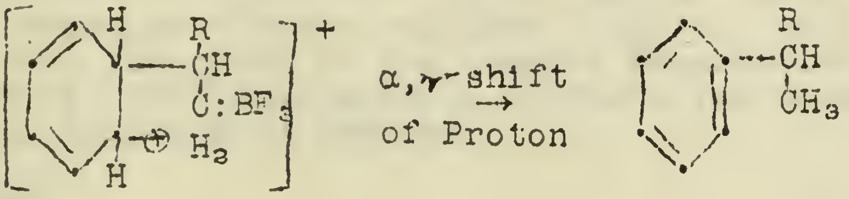


(10)

4. The final step is the elimination of a proton to restore the aromatic ring structure.



(11)



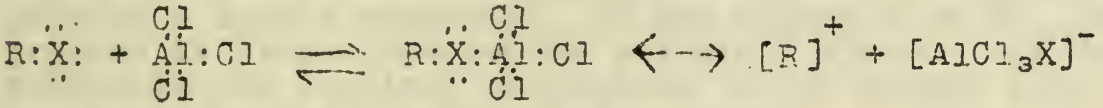
(12)

It can thus be seen that acid-catalyzed reactions, through the intermediate formation of a positive fragment, or carbonium ion, may alkylate or acylate the benzene nucleus. Analogous reactions may also occur with the enolic forms of ketones. Accordingly, the specific reactions have been largely grouped under the two headings, Alkylation reactions and Acylation reactions.

A. Alkylation Reactions:

1. With Alkyl Halides:

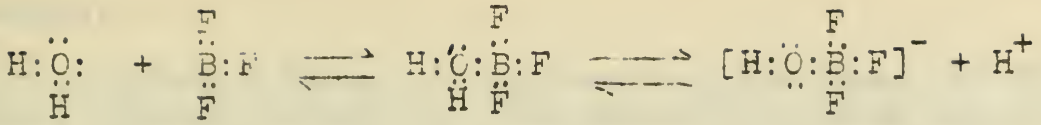
Conductance and dielectric-constant measurements indicate the formation of ionic complexes between catalyst and alkyl halide



$$R:\ddot{\underset{..}{X}}: + \overset{Cl}{\underset{Cl}{Al}}:Cl \rightleftharpoons R:\overset{..}{\underset{..}{X}}:\overset{Cl}{\underset{Cl}{Al}}:Cl \longleftrightarrow [R]^{+} + [AlCl_3X]^{-} \qquad (13)$$

Metallic halides and HF have been found to catalyze this reaction. Reaction of the latter with tertiary halides proceeds readily at 0°C. Secondary halides require a temperature of 25°C., while primary halides react only at higher temperatures; 80°C. This parallels the ease of carbonium ion formation from 1°, 2°, and 3° carbon compounds. The carbonium ion which is formed reacts with the aromatic compounds as in equation (8).

BF_3 will not catalyze the alkylation of benzene by alkyl chlorides unless at least a trace of water is present. The following intermediate reaction is presumed to occur:



$$\underset{H}{H{:}\ddot{O}{:}} + \overset{F}{\underset{F}{\ddot{B}{:}F}} \rightleftharpoons \overset{\quad F}{\underset{H\ F}{H{:}\ddot{O}{:}\ddot{B}{:}F}} \rightleftharpoons [H{:}\ddot{O}{:}\overset{F}{\underset{F}{\ddot{B}}}{:}F]^- + H^+$$

(14)

$$H^+ + RCl \rightleftharpoons R{:}\underset{\cdot\cdot}{\ddot{Cl}}{:}H \rightleftharpoons [R]^+ + H{:}\underset{\cdot\cdot}{\ddot{Cl}}{:}$$

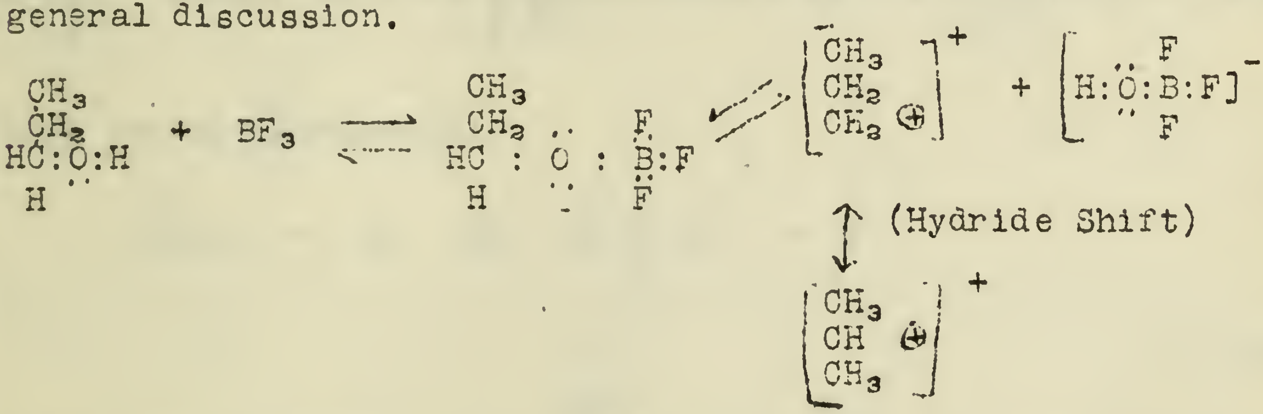
If alkyl fluorides are used instead of the chlorides, the reaction proceeds vigorously. This is attributed to the greater stability of the BF_4^- ion as compared to the BF_3Cl^- ion.

2. With Olefins:

Olefins have been used in alkylating aromatic compounds in the presence of acid catalysts such as HF, H_2SO_4, H_3PO_4, P_2O_5, BF_3, $AlCl_3$. The reaction forms a positive fragment containing the catalyst as was indicated in the general description. The self-condensation of Olefins to produce polymers was discussed in the Carbon-Carbon Double Bond Seminar.

3. With Alcohols:

Alcohols react to form carbonium ions as was pointed out in the general discussion.



$$\begin{array}{l}CH_3\\CH_2\\HC{:}\ddot{O}{:}H\\H\end{array} + BF_3 \rightleftharpoons \begin{array}{l}CH_3\\CH_2\\HC\ {:}\ \ddot{O}\ {:}\ \overset{F}{\underset{F}{\ddot{B}}}{:}F\\H\end{array} \rightleftharpoons \left[\begin{array}{l}CH_3\\CH_2\\CH_2\ \oplus\end{array}\right]^+ + \left[H{:}\ddot{O}{:}\overset{F}{\underset{F}{B}}{:}F\right]^-$$

$$\updownarrow \text{(Hydride Shift)}$$

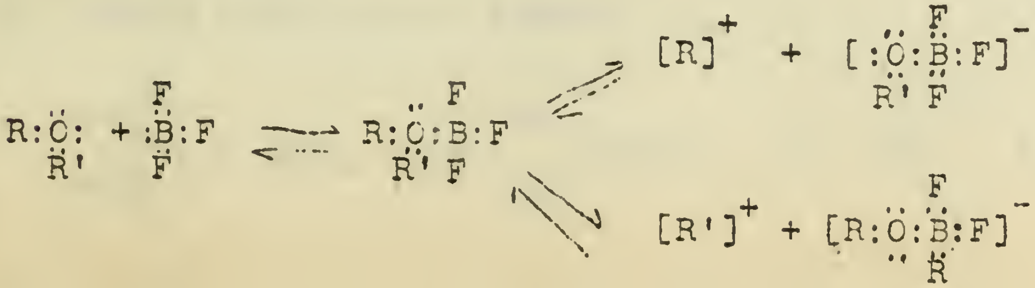
$$\left[\begin{array}{l}CH_3\\CH\ \oplus\\CH_3\end{array}\right]^+$$

(15)

Allyl alcohol is an interesting example of a compound which can undergo a double reaction. In the presence of HF, 3-phenyl-1-propene is first produced by a typical alcohol alkylation. Subsequently, an olefinic alkylation at the double bond results in the formation of 1,2-diphenyl propane.

4. With Ethers:

Either of two Carbonium ions may be formed from an ether. BF_3 and HF have been used as catalysts.

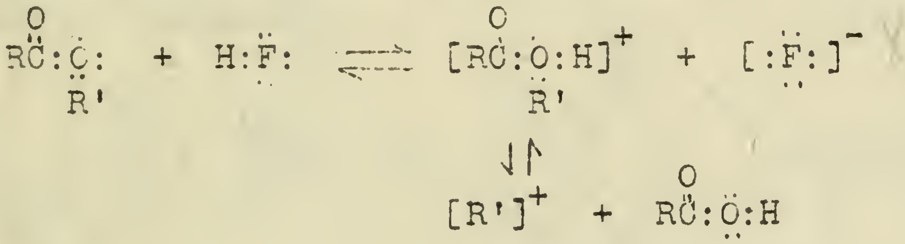


$$\underset{R'}{R{:}\ddot{O}{:}} + \overset{F}{\underset{F}{{:}B{:}F}} \rightleftharpoons \overset{\quad F}{\underset{R'\ F}{R{:}\ddot{O}{:}B{:}F}} \begin{array}{l}\rightleftharpoons [R]^+ + [{:}\ddot{O}{:}\overset{F}{\underset{F}{\ddot{B}}}{:}F]^- \ (\text{with } R' \text{ on } O)\\ \rightleftharpoons [R']^+ + [R{:}\ddot{O}{:}\overset{F}{\underset{R}{\ddot{B}}}{:}F]^-\end{array}$$

(16)

5. With Esters:

Esters of aliphatic types of compounds may be used for the alkylation type of reaction. This was illustrated earlier. If HF is used instead of BF_3, the mechanism is identical:

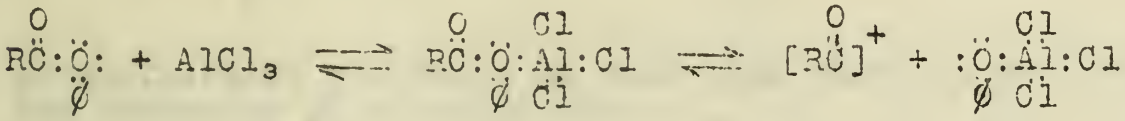


$$\overset{O}{R\ddot{C}}:\underset{R'}{\ddot{O}}: + H:\ddot{F}: \rightleftharpoons [\overset{O}{R\ddot{C}}:\underset{R'}{O}:H]^+ + [:\ddot{F}:]^- \rightleftharpoons [R']^+ + \overset{O}{R\ddot{C}}:\ddot{O}:H \qquad (17)$$

B. Acylation Reactions.

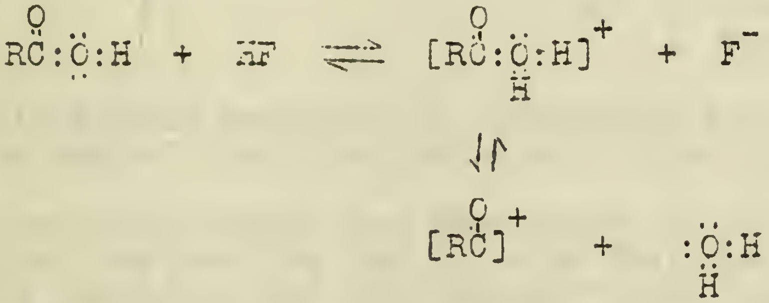
1. With Esters:

Acylation by aromatic esters, as previously mentioned, can be catalyzed by $AlCl_3$, BF_3, metallic halides and H-acids. A possible mechanism is:



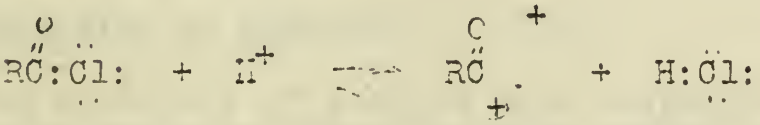
$$\overset{O}{R\ddot{C}}:\underset{\phi}{\ddot{O}}: + AlCl_3 \rightleftharpoons \overset{O}{R\ddot{C}}:\underset{\phi}{\ddot{O}}:\overset{Cl}{\underset{Cl}{Al}}:Cl \rightleftharpoons [\overset{O}{R\ddot{C}}]^+ + :\underset{\phi}{\ddot{O}}:\overset{Cl}{\underset{Cl}{\dot{A}l}}:Cl \qquad (18)$$

2. With Carboyx Compounds:



$$\overset{O}{R\ddot{C}}:\ddot{O}:H + HF \rightleftharpoons [\overset{O}{R\ddot{C}}:\underset{H}{\ddot{O}}:H]^+ + F^- \rightleftharpoons [\overset{O}{R\ddot{C}}]^+ + :\underset{H}{\ddot{O}}:H \qquad (19)$$

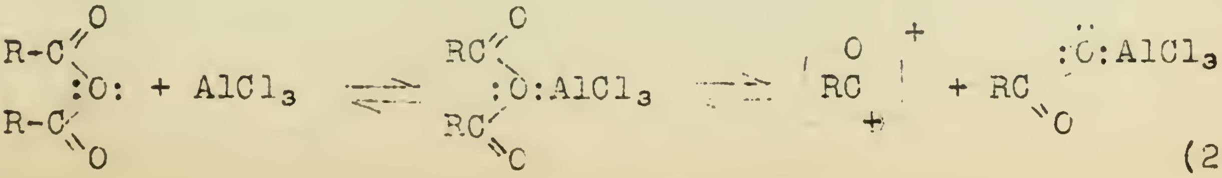
3. With Acyl Halides:



$$\overset{O}{R\ddot{C}}:\ddot{Cl}: + H^+ \rightleftharpoons \overset{O}{RC}^+ + H:\ddot{Cl}: \qquad (20)$$

4. With Carboxy Anhydrides:

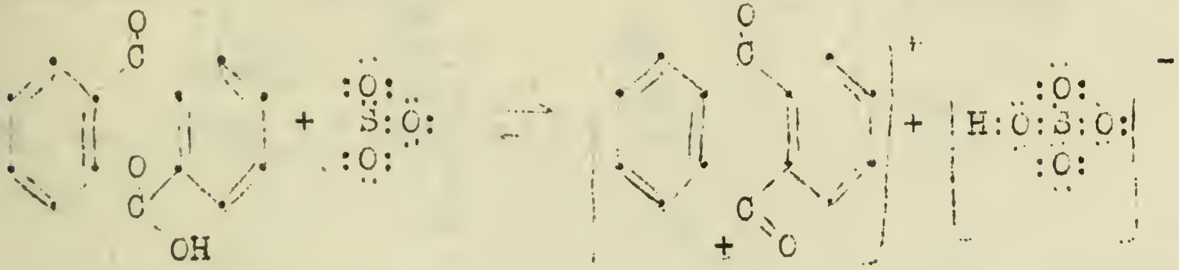
a. Simple acylation of Benzene



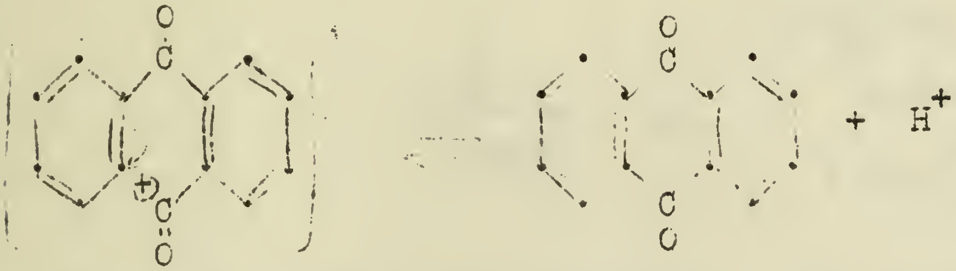
$$\begin{matrix}R\text{-}C(=O)\\ :\ddot{O}:\\ R\text{-}C(=O)\end{matrix} + AlCl_3 \rightleftharpoons \begin{matrix}RC(=O)\\ :\ddot{O}:AlCl_3\\ RC(=O)\end{matrix} \rightleftharpoons \overset{O}{RC}^+ + RC(=O)\ddot{O}:AlCl_3 \qquad (21)$$

b. Cyclic Ketone Formation

The cyclization of aromatic carboxylic compounds to form cyclic ketones can be effected by such acids as $AlCl_3$, $SnCl_4$, HF, H_2SO_4 and P_2O_5. When the reaction is carried out in a H_2SO_4-SO_3 solution the rate of condensation increases as the amount of SO_3 is increased. Mechanism:

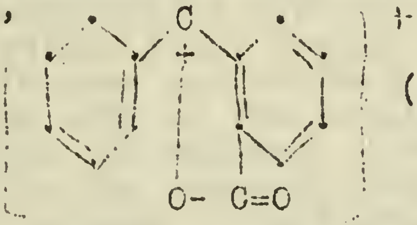


(22)



(23)

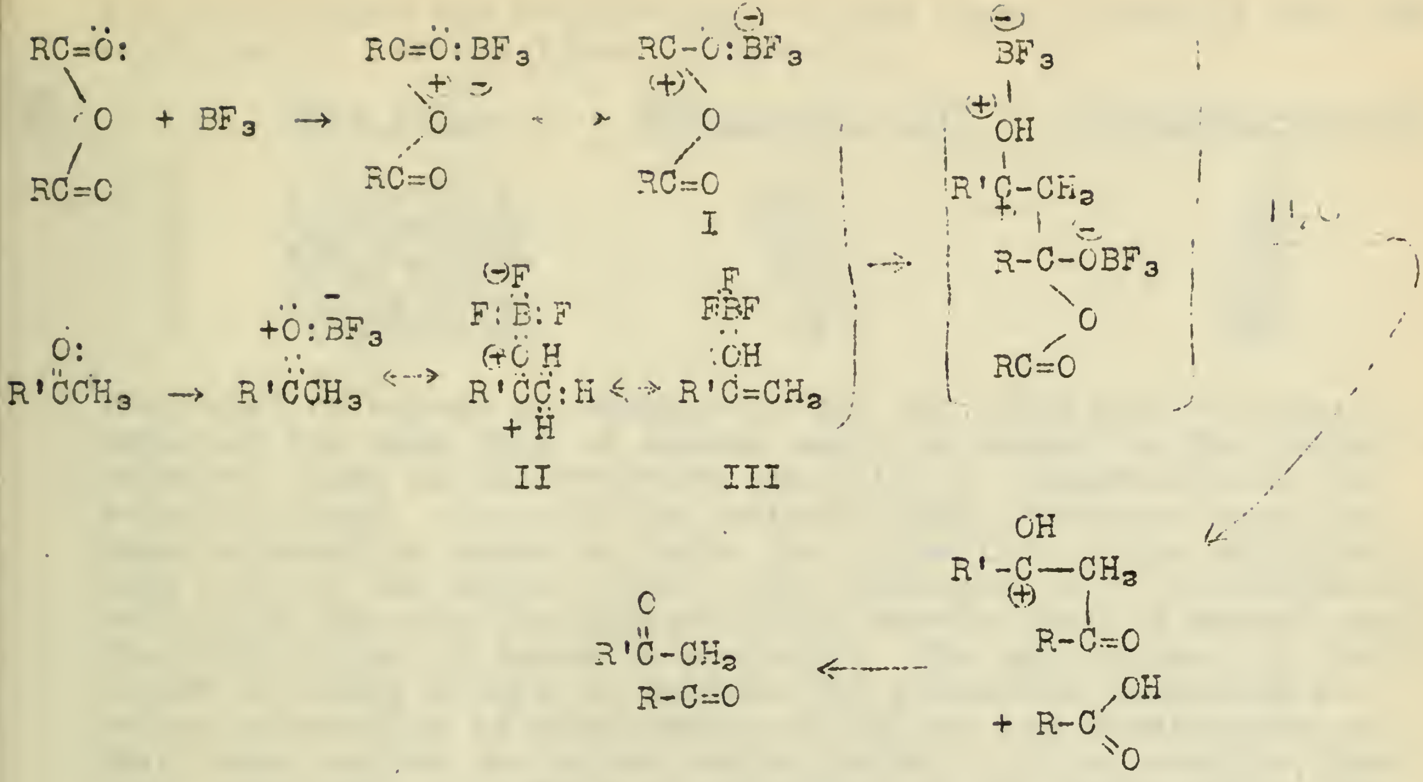
In cyclization reactions of this kind there is good evidence for the formation of a cyclic ion, (equation (22), but this should probably be considered as a side reaction rather than as one of the intermediates in the formation of anthraquinone.



The condensation has been shown to be a first order reaction. A logical explanation for this is that the carbonium ion is formed rapidly (equation 22) and therefore the rate determining step is that shown in equation 23, which is obviously first order.

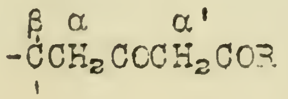
c. Acylation of Ketones

The acylation of ketones with aliphatic anhydrides in the presence of boron trifluoride is an example of an acid-catalyzed Claisen reaction. Although the mechanism of the reaction is not entirely clear, it has been postulated to take place in the following manner;



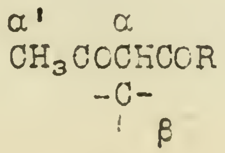
Coordination of boron trifluoride with oxygen in the anhydride and in the ketone initiates this reaction. The active form of the anhydride (I) (which may be considered a form of carbonium ion) condenses with the activated ketone (III) (which is shown as an enol) to form one mole of β-diketone and one mole of acid. The coordination complex (I) is the same as the proposed intermediate in the Friedel-Crafts synthesis. It appears, however, that the ketone must also be activated by the coordination of boron trifluoride, since this catalyst appears to be necessary to effect the condensation. The reaction cannot be carried out using either boron trichloride or aluminum chloride, even under the most favorable conditions, although these are excellent catalysts for the Friedel-Crafts reaction. It is not certain that form (III) really represents the activated ketone; it can at least be said that the coordination of boron trifluoride with the ketone results in an electronic redistribution within the molecule which produces a very active hydrogen compound which can condense with the anhydride. In the ketone complex, hydrogen bonding between fluorine and hydrogen on the carbon adjacent to the carbonyl carbon may help this process.

The acylation of unsymmetrical ketones of the type $-\underset{\beta}{C}\underset{\alpha}{C}H_2C\underset{\alpha'}{C}H_3$ with $(RCC)_2C$ may produce the following isomeric β-diketones.



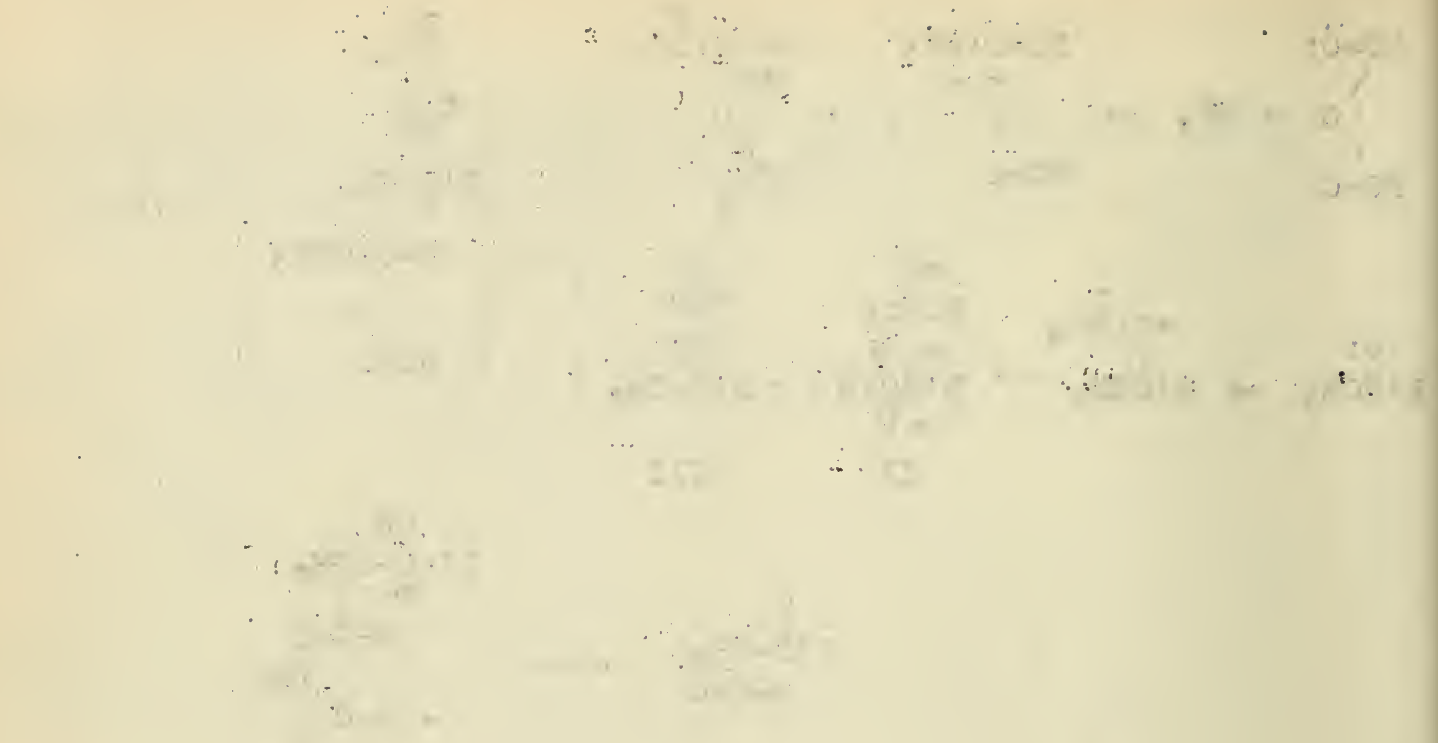
$-\overset{\beta}{C}\overset{\alpha}{C}H_2C\overset{\alpha'}{C}CH_2COR$

Methyl-acyl
(IV)



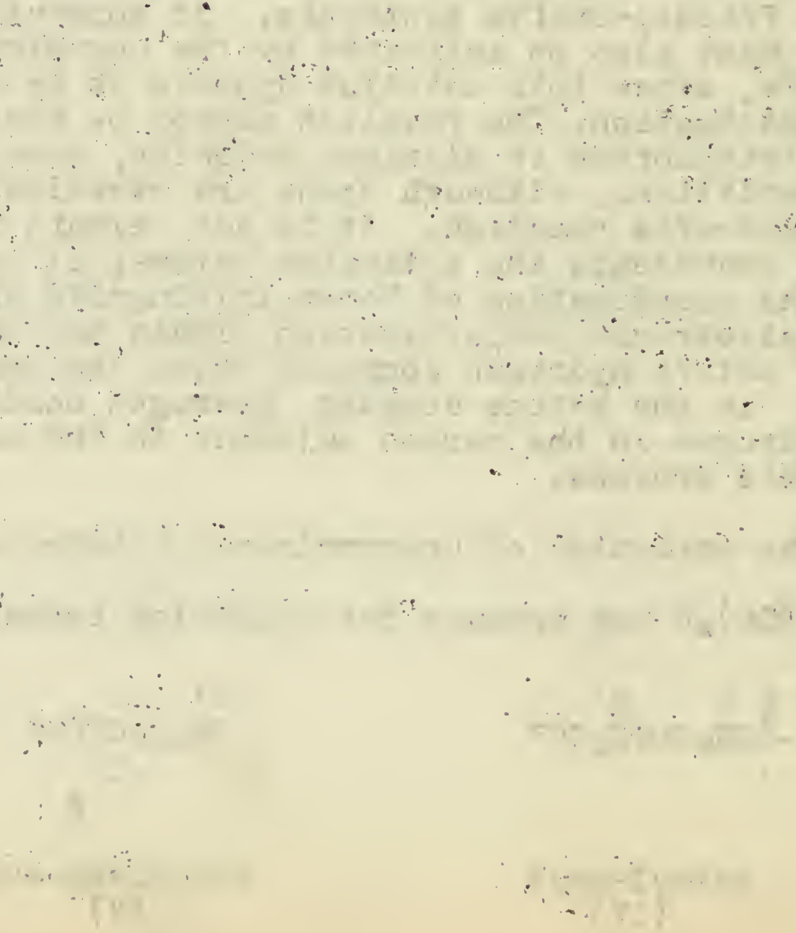
$\overset{\alpha'}{C}H_3CC\underset{\substack{-C-\\ \beta}}{\overset{\alpha}{C}}HCOR$

Methylene-acyl
(V)



coordination is [illegible] with [illegible] and in the [illegible]. The [illegible] of [illegible] [illegible] conjugation with the [illegible] [illegible] [illegible] in the [illegible] [illegible] data are evident.

The reduction of [illegible] [illegible]



The table gives the proportions of each isomer obtained from the acylation of various types of ketones.

	Type Ketone	Methyl-acyl (IV)	Methylene-acyl (V)
A	$R_3CCH_2COCH_3$	100%	0%
B	$R_2CHCH_2COCH_3$	55%	45%
C	$RCH_2CH_2COCH_3$	10%	90%
D	$CH_3CH_2COCH_3$	0%	100%
E	$C_6H_5CH_2COCH_3$	2%	98%

The relative amount of methylene-acyl and methyl-acyl product obtained for each type of ketone seems to depend on the number of hydrogen atoms on the β-carbon atom; it is independent of the anhydride used. The results indicate that, whenever possible, hyperconjugation seems to favor the formation of the methylenic enol form of the ketone which then condenses with the anhydride. Certain of the results indicate that steric factors cannot explain the proportions of isomeric products. The application of the $-I_s$ effect of alkyl groups to explain the preferred direction of ketone activation is unsatisfactory, since any predictions on this basis oppose the experimental facts. It is possible, however, that the $-I_s$ effect is important in the cases where the hyperconjugation effects are weak (Type A and B ketones) and the methylenic hydrogens are so deactivated that only the methyl hydrogens may be activated by the boron trifluoride as it coordinates with the ketone.

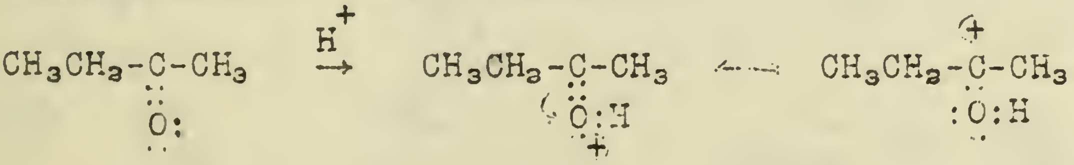
C. Addition Reactions of Carbonyl Compounds.

As has been previously mentioned in the seminar of August 15, 1947, the reactions of aldehydes with hydroxylamine, hydrazines, and semicarbazides are catalyzed by acids.

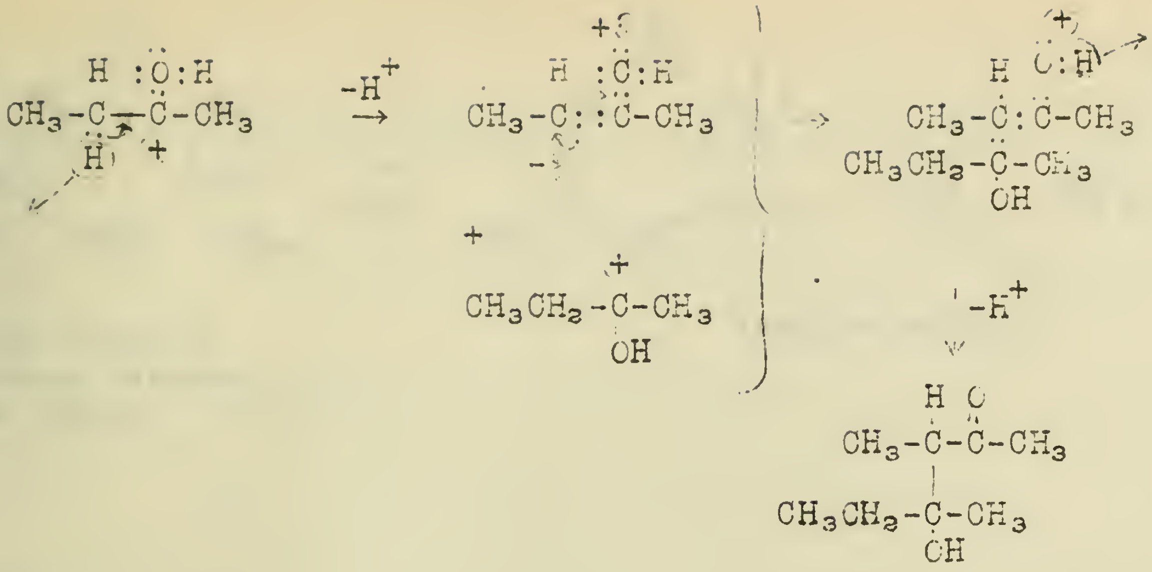
D. Acetal Formation.

These reactions are to be discussed in the seminar of August 22, 1947. They are also a type of acid-catalyzed reactions.

E. Acid-Catalyzed Aldol Condensation.



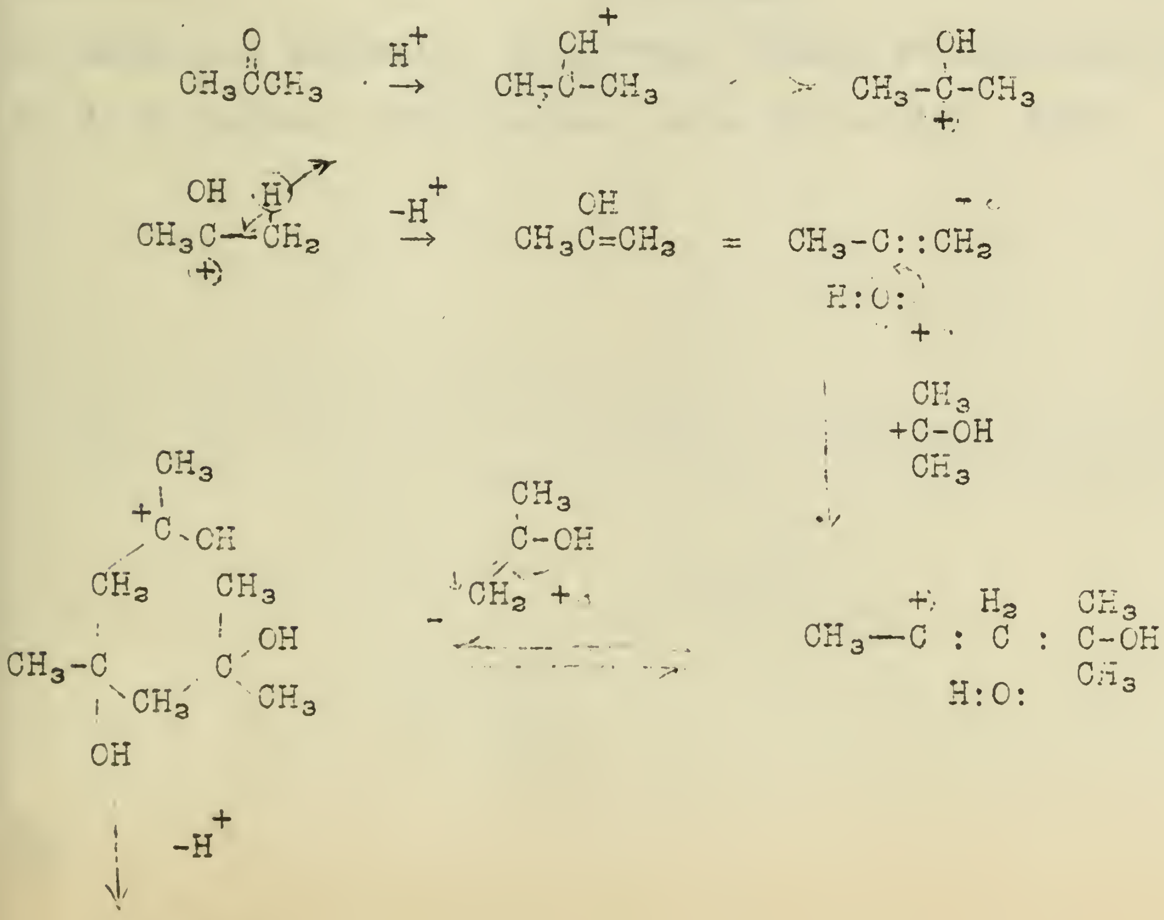
$$CH_3CH_2\text{-}\underset{\ddot{O}:}{C}\text{-}CH_3 \xrightarrow{H^+} CH_3CH_2\text{-}\underset{\overset{+}{\ddot{O}}:H}{C}\text{-}CH_3 \longleftarrow CH_3CH_2\text{-}\overset{+}{\underset{:O:H}{C}}\text{-}CH_3$$

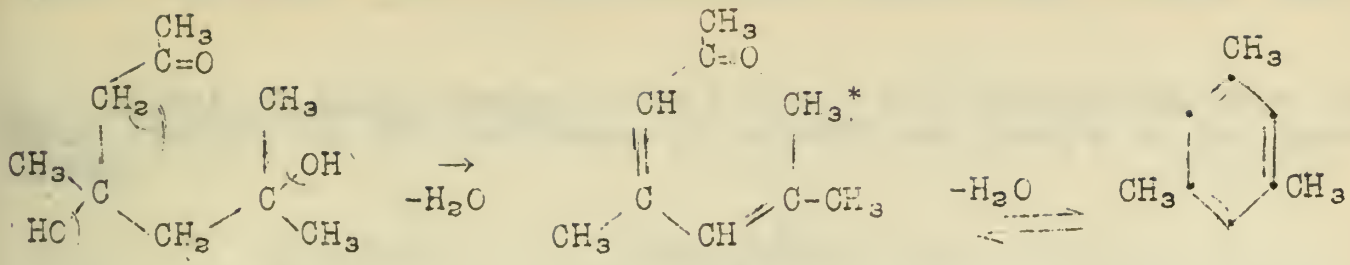


This reaction has been included under a separate heading although it falls under the general heading of "Alkylation." As in other acid-catalyzed condensations, the mechanism involves the formation of a carbonium ion. This is followed by an electrophilic attack of the carbonium ion on the enol form of the carbonyl compound (i.e., an olefin). The direction of enolization can be predicted by the theory of hyperconjugation.

F. 1,3,5-Trisubstituted Benzene Formation.

The formation of mesitylene from acetone is an acid-catalyzed reaction.





β-and vinyl-β-
hydroxy ketones
lose water

*active methyl

Summary.

The characteristic effect of the acid catalyst is the increase in concentration of the carbonium ion involved in the reaction. This is usually accomplished by the electrophilic displacement of one acid by another. In some reactions the combination of the acid with the reacting substance serves to localize the electron deficiency on one atom, which can then behave as an acid.

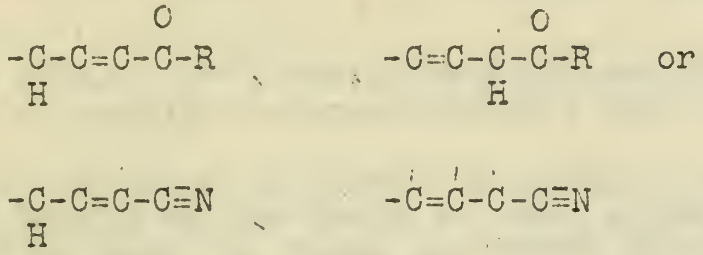
References

1. Luder and Zuffanti, "Electronic Theory of Acids and Bases."

2. H. G. Walker, Dissertation, Duke University, 1946.

ALKALI CATALYZED α,β-β,γ EQUILIBRIUM OF UNSATURATED CARBONYL COMPOUNDS

Effect of Alkyl Groups.--The α,β-β, equilibrium has been carefully studied for the influence of substituent groups in the general system

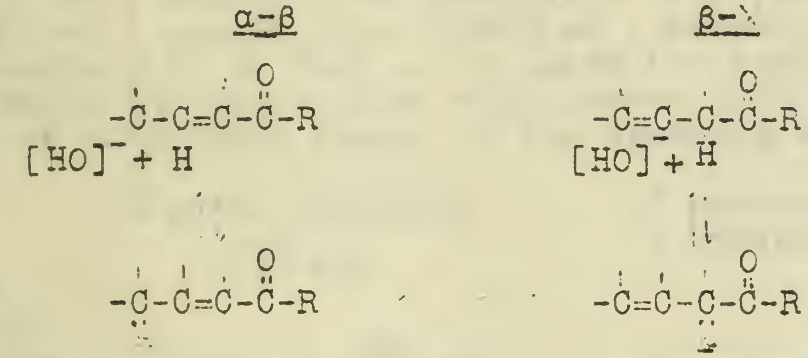


$$-\underset{H}{C}-C=C-\overset{O}{C}-R \qquad -C=C-\underset{H}{C}-\overset{O}{C}-R \quad \text{or}$$

$$-\underset{H}{C}-C=C-C\equiv N \qquad -C=C-C-C\equiv N$$

where R = H, alkyl, hydroxyl, or alkoxyl.

The reaction undoubtedly proceeds by the removal of the hydrogen atom on a carbon atom α to another holding a double bond, followed by subsequent recombination with a proton.

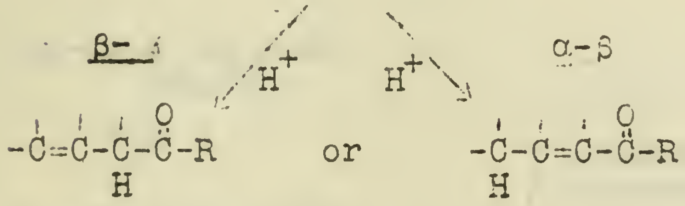


$$\underline{\alpha-\beta} \qquad\qquad \underline{\beta-\gamma}$$

$$[HO]^- + \underset{H}{-C}-C=C-\overset{O}{\ddot{C}}-R \qquad [HO]^- + -C=C-\underset{H}{C}-\overset{O}{\ddot{C}}-R$$

$$-\underset{\cdot\cdot}{C}-C=C-\overset{O}{\ddot{C}}-R \qquad -C=C-\underset{\cdot\cdot}{C}-\overset{O}{\ddot{C}}-R$$

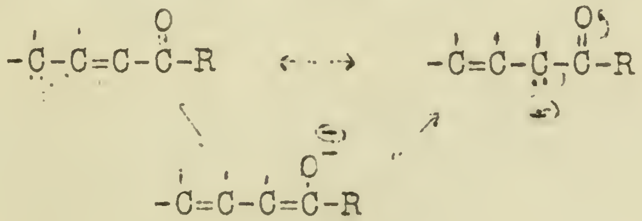
Identical



$$\underline{\beta-\gamma} \quad H^+ \qquad H^+ \quad \alpha-\beta$$

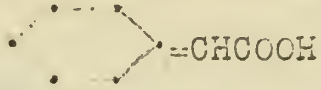
$$-C=C-\underset{H}{C}-\overset{O}{\ddot{C}}-R \quad \text{or} \quad -\underset{H}{C}-C=C-\overset{O}{\ddot{C}}-R$$

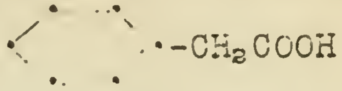
It will be observed that the carbanion which is formed in either case is the same since the forms written differ only in the distribution of electrons. The carbanion is thus a resonance hybrid of the forms.



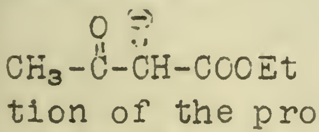
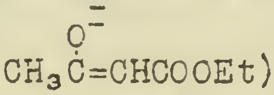
$$-\underset{\cdot\cdot}{C}-C=C-\overset{O}{\ddot{C}}-R \longleftrightarrow -C=C-\underset{\cdot\cdot}{C}-\overset{O}{\ddot{C}}-R$$

$$-C=C-C=\overset{O^-}{C}-R$$

Clearly the ease with which the intermediate is formed (and therefore the ease of establishing equilibrium) will depend on the factors already discussed under "Carbanion Formation" ("Carbanion Addition to Carbonyl Compounds," p. 2). This is well illustrated by the fact that the acids 

and 

require hot alkali for interconversion, yet the analogous methyl ketones are so readily interconvertible that separation is difficult.

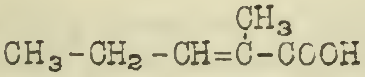
While it is often difficult to predict the point of addition to a resonance hybrid on the basis of what appears to be the most probable structure when the forms are quite dissimilar, (cf. 
$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\ominus}{C}H-COOEt$
and 
$CH_3\overset{O^-}{\overset{|}{C}}=CHCOOEt$), in this particular case the addition of the proton seems to follow the rules governing the location of the double bond which were discussed under "Elimination Reactions." In other words, although the α,β position is the more probable position for a double bond (because of the conjugation with the carbonyl or nitrile group), the effect of introducing alkyl groups into the molecule will be such as to shift the equilibrium in that direction in which the double bond will become conjugated with the largest number of α hydrogen atoms. A few examples will illustrate the point.

α alkyl groups

$CH_3-CH_2-CH=CHCOOH$

75% α,β

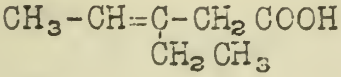
2 hyperconjugation forms α,β
5 hyperconjugation forms β,γ


$CH_3-CH_2-CH=\overset{\overset{CH_3}{|}}{C}-COOH$

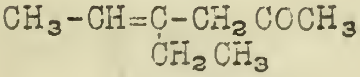
81% α,β

5 hyperconjugation forms α,β
4 hyperconjugation forms β,γ

β alkyl groups

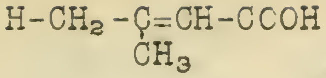

$CH_3-CH=\underset{\underset{CH_2CH_3}{|}}{C}-CH_2COOH$

95% β,γ


$CH_3-CH=\underset{\underset{CH_2CH_3}{|}}{C}-CH_2COCH_3$

86% β,γ

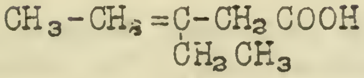
4 hyperconjugation forms α,β
7 hyperconjugation forms β,γ


$H-CH_2-\underset{CH_3}{C}=CH-CCOH$

100% α,β,

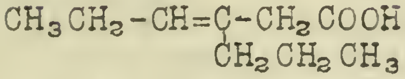
6 hyperconjugation forms α,β
5 hyperconjugation forms β,γ

γ
alkyl
groups


$CH_3-CH_2=\underset{CH_2CH_3}{C}-CH_2COOH$

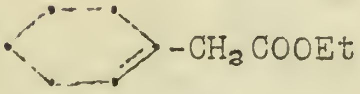
95% β, γ

4 hyperconjugation forms α,β
7 hyperconjugation forms β, γ


$CH_3CH_2-CH=\underset{CH_2CH_2CH_3}{C}-CH_2COOH$

67% β, γ

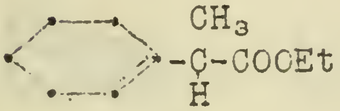
4 hyperconjugation forms α,β
6 hyperconjugation forms β,γ



62% β, γ

4 hyperconjugation forms α,β
6 hyperconjugation forms β,γ

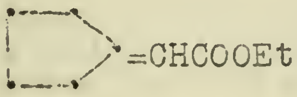
Cyclo-
hexyl
groups



95% β,γ

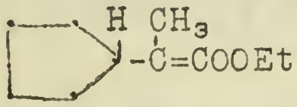
7 hyperconjugation forms α,β
5 hyperconjugation forms β,γ

It is obvious from an examination of these examples that the relationship is only qualitative, but of a quite general nature. The reason for the anomaly in the last case is not known. It is not observed with the corresponding cyclopentyl derivative.



60% α,β

4 hyperconjugation forms α,β
6 hyperconjugation forms β,γ

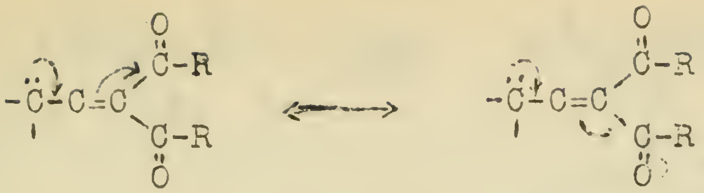


88% α,β

7 hyperconjugation forms α,β
5 hyperconjugation forms β,γ

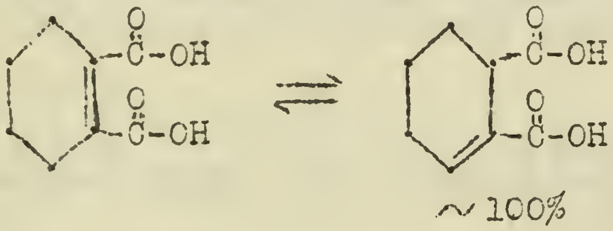
Substitution of a Second Activating Group

α-Substitution.--Introduction of a carbonyl group on the α carbon atom puts both carbonyl groups into conjugation with the double bond. Since both of these groups tend to polarize the double bond in the same direction the α,β position is favored.

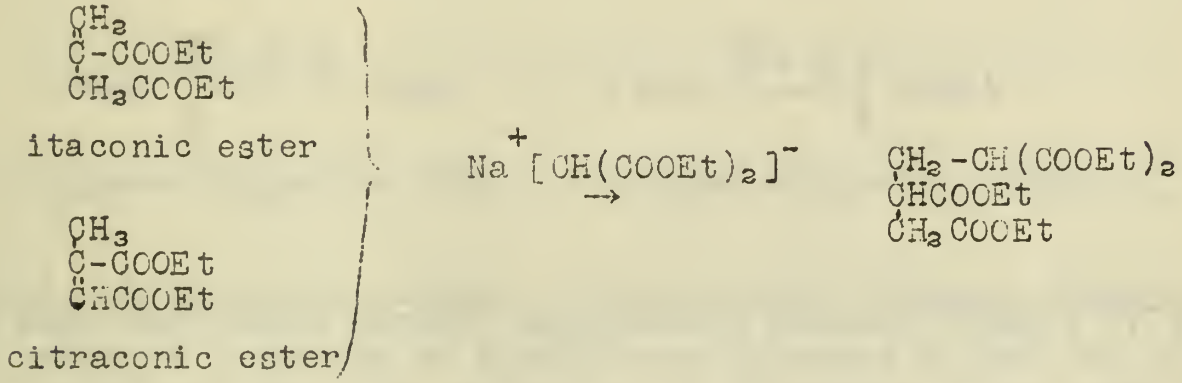


It is well known that the Knoevenagel reaction with ethyl malonate usually produces α,β unsaturated compounds.

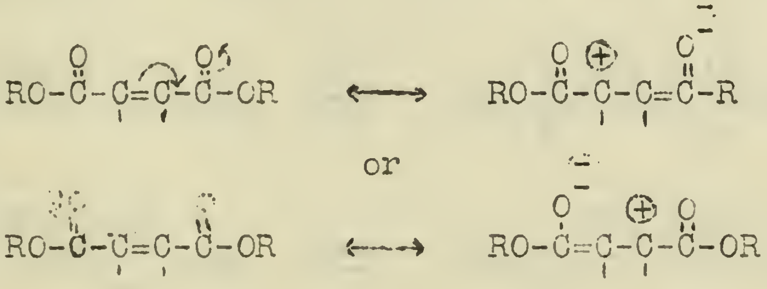
β-Substitution.--The well known reactions of itaconic and citraconic acid and the behavior of the tetrahydrophthalic acids are examples of the β substitution of an activating group into the system. β,γ unsaturation is favored.



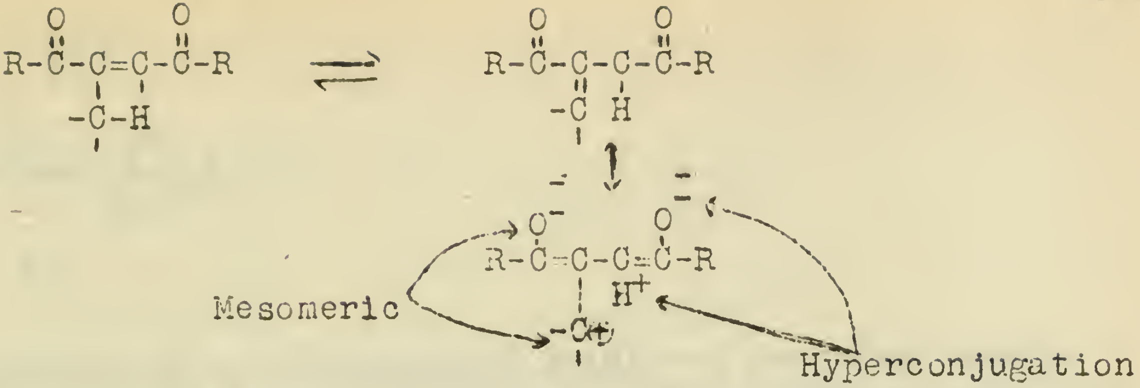
~100%



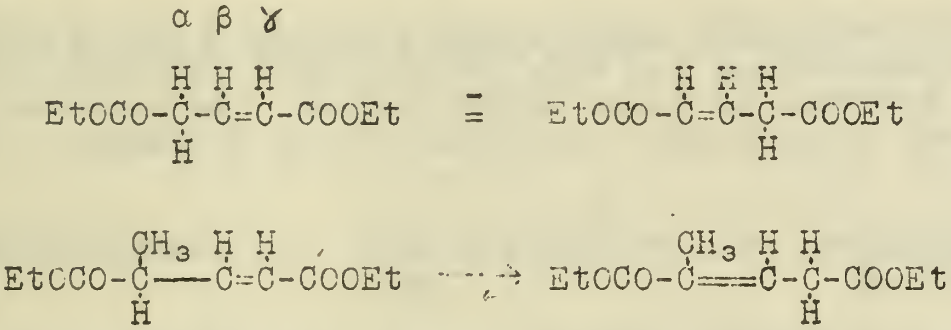
Migration of the double bond into the β,γ position is favored because the activating groups are in opposition and only one of them can be involved in a mesomeric or electromeric shift at a time.



Obviously either of these resonance forms requires the presence of a positive charge on an atom which cannot well accomodate it. Hence the β,γ form is favored since this form allows the development of a plus charge on an atom better able to accomodate it with one carbonyl group and a simultaneous hyperconjugation form with the other.



γ-Substitution.--Provided that the activating groups are the same, the α,β and β,γ positions are indentical in a system of this kind until an alkyl group is introduced. When alkylation has taken place that form will be favored which allows the most hyperconjugation forms. The alkylation of glutaconic ester is an example.

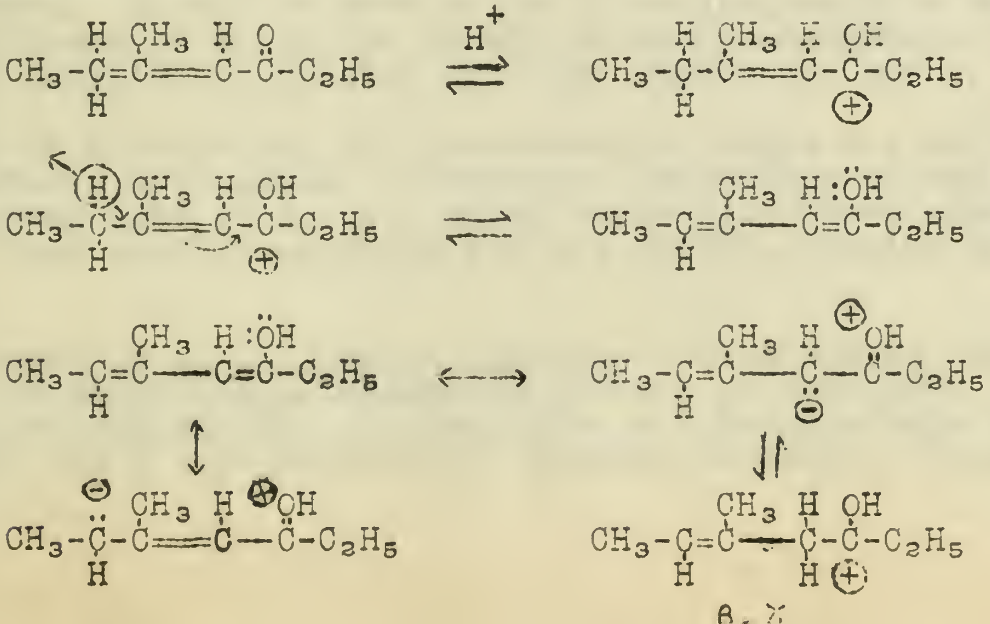


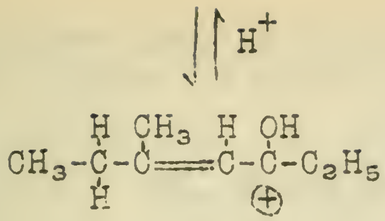
$$\overset{\alpha}{} \; \overset{\beta}{} \; \overset{\gamma}{} \quad EtOCO-\overset{H}{\underset{H}{C}}-\overset{H}{C}=\overset{H}{C}-COOEt \;=\; EtOCO-\overset{H}{C}=\overset{H}{C}-\overset{H}{\underset{H}{C}}-COOEt$$

$$EtCCO-\overset{CH_3}{\underset{H}{C}}-\overset{H}{C}=\overset{H}{C}-COOEt \longrightarrow EtOCO-\overset{CH_3}{C}=\overset{H}{C}-\overset{H}{\underset{H}{C}}-COOEt$$

1 hyperconjugation form 5 hyperconjugation forms

Acid Catalyzed Equilibrium of Unsaturated Carbonyl Compounds.--It has been shown that certain unsaturated ketones capable of tautomerism could be converted to equilibrium mixtures by the aid of mineral acids and that the proportion of tautomers formed was the same as that produced in alkaline media. Equilibrium is established much more slowly in this case and presumably the mechanism is that of general acid-induced enolization: (Tautomerism and Carbanion Formation, p. 1)





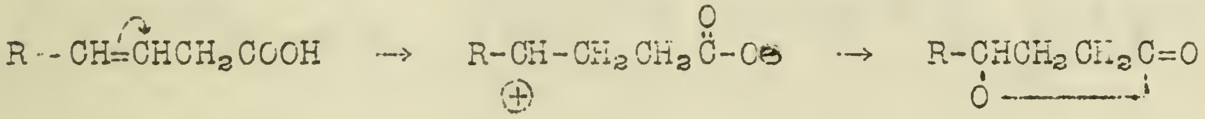
$$\Big\downarrow\Big\uparrow H^+$$

$$CH_3-\overset{H}{\underset{H}{C}}-\overset{CH_3}{C}=\overset{H}{C}-\overset{OH}{\underset{\oplus}{C}}-C_2H_5$$

α,β

Lactonization of α,β Unsaturated Acids.--A reaction closely related to the α,β and β,γ equilibrium of unsaturated carbonyl compounds is the γ lactonization of α,γ unsaturated acids on treatment with hot dilute sulfuric acid. The ease of this transformation will depend on the rate of α,β to β,γ change and also the rate of lactonization. It is interesting, therefore, to consider the effects of alkyl substitution into such molecules in the light of the preceding discussion.

1.) Acids with one γ and no β alkyl group ($RCH_2-CH=CHCOOH$). Both changes have been found to be slow but lactonization is faster than tautomerism. Lactonization would be expected to proceed readily because R should facilitate addition to the double bond.



$$R-CH=CHCH_2COOH \rightarrow R-\underset{\oplus}{CH}-CH_2CH_2\overset{O}{C}-O^{\ominus} \rightarrow R-\underset{O}{CH}CH_2CH_2C=O$$

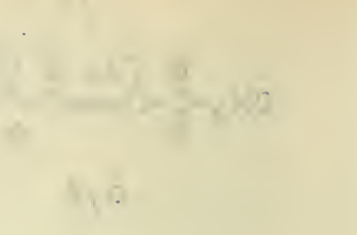
2.) Acids with two γ alkyl groups ($R_2CHCH=CHCOOH$). Lactonization is fast and tautomerism is slow. This is an even more favorable case than 1.) for addition to a double bond.

3.) Acids with one γ and one β alkyl group ($RCH_2\overset{R}{C}=CHCOOH$). Lactonization is slower than tautomerism. This is somewhat surprising since usually the more highly substituted ethylene is the more rapidly it undergoes addition reactions.

4.) Acids with no γ substituents ($CH_3-\overset{R}{C}=CHCOOH$). Tautomerism is fast and irreversible in the direction $\beta,\gamma \rightarrow \alpha,\beta$. No lactonization occurs. As can be seen in the preceding section this is one of the cases in which the number of hyperconjugation forms for the α,β position is greater than the number for the β,γ position.

It is interesting that treatment of types 1.) and 2.) with cold 60% sulfuric acid gives a convenient separation of the α,β from the β,γ unsaturated acid. β,γ Acids lactonize almost quantitatively under these conditions while the α,β isomers require heat.

Formation of Conjugated Olefins.--Occasionally during the preparation of diolefins a conjugated product is obtained. Thus in the exhaustive methylation of piperidine a 1,4-pentadiene would be expected but 1,3-pentadiene is actually isolated. Presumably this



[illegible]

1.) [illegible]

[illegible]

2.) [illegible]

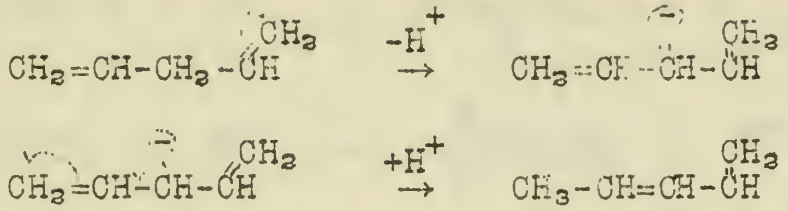
3.) [illegible]

4.) [illegible]

[illegible]

[illegible]

is another example of an $\alpha,\beta-\beta,\gamma$ equilibrium in which one of the olefin groups is fulfilling the function of an activating group.



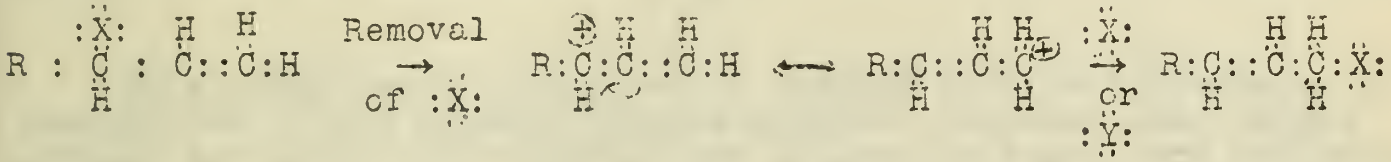
$$CH_2{=}CH{-}CH_2{-}\overset{CH_2}{CH} \xrightarrow{-H^+} CH_2{=}CH{-}CH{-}\overset{CH_3}{CH}$$

$$CH_2{=}CH{-}CH{-}\overset{CH_2}{CH} \xrightarrow{+H^+} CH_3{-}CH{=}CH{-}\overset{CH_3}{CH}$$

As mentioned above, when the γ position is unsubstituted the double bond is favored in the α,β position (see the example given in the section "Effect of Alkyl Groups").

Migration of Double Bonds in the Allylic System

Many reactions involving the allylic system are known in which rearrangement and a shift of the double bond occurs. The general process may be explained as follows:



$$R:\overset{:X:}{\underset{H}{C}}:\overset{H}{C}::\overset{H}{C}:H \xrightarrow[\text{of } :X:]{\text{Removal}} R:\overset{\oplus}{\underset{H}{C}}:\overset{H}{C}::\overset{H}{C}:H \longleftrightarrow R:\underset{H}{C}::\overset{H}{C}:\overset{H}{\underset{H}{C^{\oplus}}} \xrightarrow[\text{or } :Y:]{:X:} R:\underset{H}{C}::\overset{H}{C}:\overset{H}{\underset{H}{C}}:X:$$

X leaves the system with an ease dependent in part on the capacity of the R group for electron release to supply electrons to the depleted carbon atom. A study of a number of such systems where R is p-chlorophenyl, p-tolyl, phenyl, methyl, etc., shows that the order is

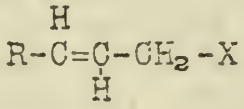
$$\underline{p}\text{-}ClC_6H_4 > \underline{p}\text{-}CH_3C_6H_4 > C_6H_5 > CH_3 > H$$

In these systems X will assume the position adjacent to the least electron releasing of the terminal groups, or what is the same thing, the double bond will become conjugated with the most electron releasing group.

Specific Reactions of the Allylic System

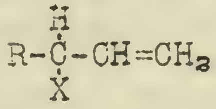
1. Formation and Hydrolysis of Allyl Halides.

Work on nucleophilic replacement reactions of allylic systems of types I and II below indicates that bimolecular SN^2 reactions pro-



$$R{-}\overset{H}{C}{=}\underset{H}{C}{-}CH_2{-}X$$

I

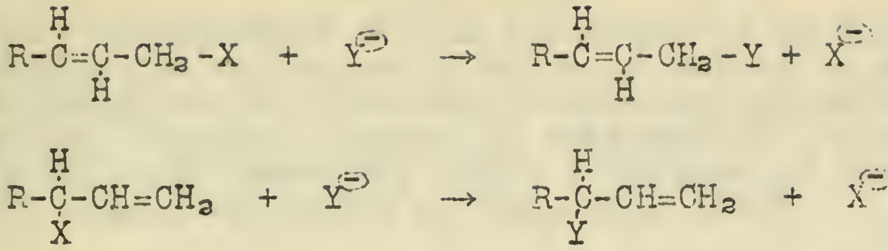


$$R{-}\overset{H}{\underset{X}{C}}{-}CH{=}CH_2$$

II

duce unrearranged products, while unimolecular or SN^1 type reactions, involving a carbonium ion intermediate, lead to a mixture of allylic isomers.

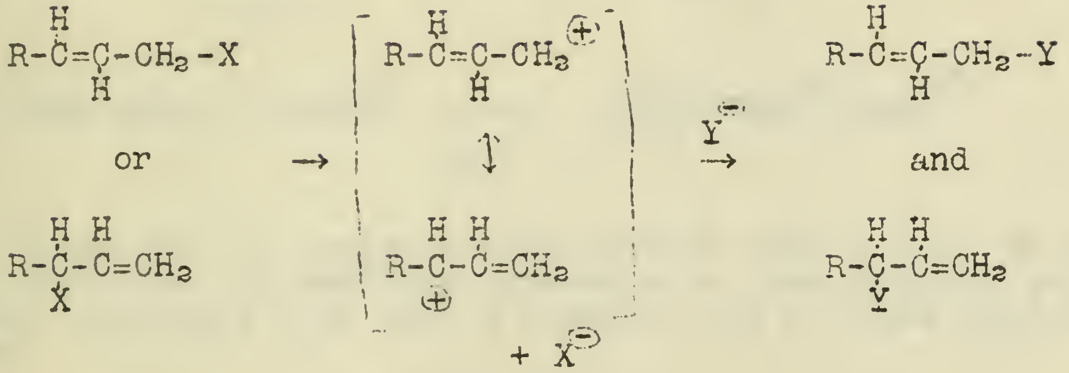
(1) SN^2



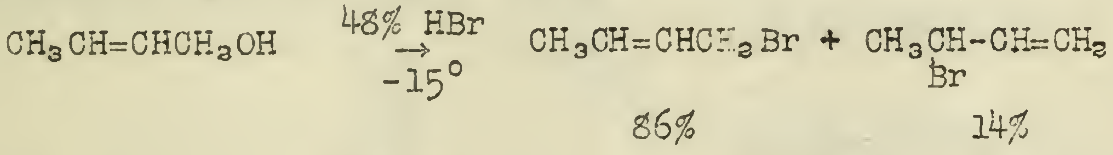
$$R{-}\overset{H}{C}{=}\underset{H}{C}{-}CH_2{-}X + Y^{\ominus} \rightarrow R{-}\overset{H}{C}{=}\underset{H}{C}{-}CH_2{-}Y + X^{\ominus}$$

$$R{-}\overset{H}{\underset{X}{C}}{-}CH{=}CH_2 + Y^{\ominus} \rightarrow R{-}\overset{H}{\underset{Y}{C}}{-}CH{=}CH_2 + X^{\ominus}$$

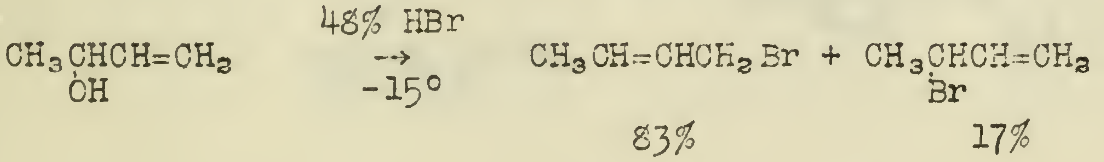
(2) SN^1



This mechanism was proposed to account for the differences in composition of the butenyl bromide mixtures observed when crotyl alcohol and methylvinylcarbinol are allowed to react with HBr under controlled conditions. The reaction is considered to be composed of two simultaneous processes. Process (1), a normal substitution reaction, gives only primary bromide from primary alcohol and secondary bromide from secondary alcohol; process (2), involving a resonating carbonium ion, gives the same mixture of bromides from both alcohols. The net result of the simultaneous operation of these two processes is a small difference in the primary bromide content of the mixtures prepared from the two alcohols by standard methods.



$$CH_3CH{=}CHCH_2OH \xrightarrow[-15^\circ]{48\%\ HBr} \underset{86\%}{CH_3CH{=}CHCH_2Br} + \underset{14\%}{CH_3\underset{Br}{CH}{-}CH{=}CH_2}$$

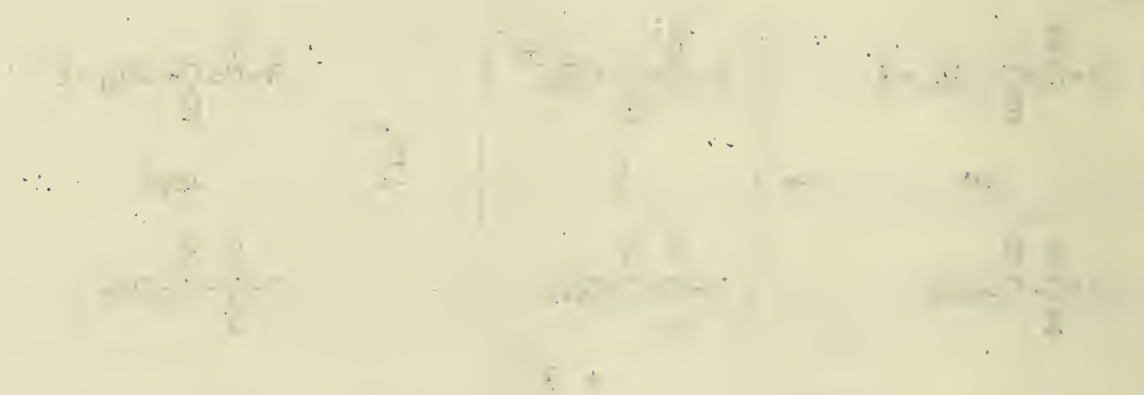


$$CH_3\underset{OH}{CH}CH{=}CH_2 \xrightarrow[-15^\circ]{48\%\ HBr} \underset{83\%}{CH_3CH{=}CHCH_2Br} + \underset{17\%}{CH_3\underset{Br}{CH}CH{=}CH_2}$$

A study of the kinetics of the hydrolysis of the two isomeric butenyl chlorides showed that methylvinylcarbinyl chloride is hydrolyzed in dilute basic media by a first order reaction, giving rise to a mixture of alcohols. Crotyl chloride reacts by a mixed first and second order process to give mixtures of alcohols, but the relative amount of normal product may be increased by raising the base concentration.

[illegible]

[illegible]



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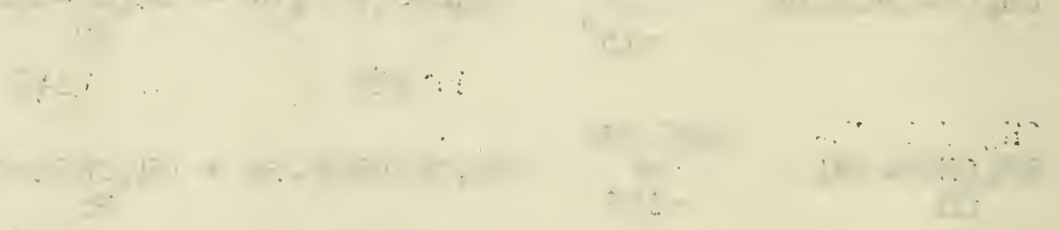

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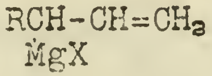
The Nature and Reactions of Allylic Grignard Reagents

The determination of the structure of an allylic Grignard reagent and the mechanism by which it reacts is an extremely complex problem which has not yet been completely resolved. Depending upon whether the Grignard reagent is covalent or ionic it could be all primary (I), all secondary (II), a mixture of these two forms, or an ionic resonance hybrid of them both (III).

$RCH{=}CHCH_2MgX$

I



$$\underset{MgX}{RCH}{-}CH{=}CH_2$$

II

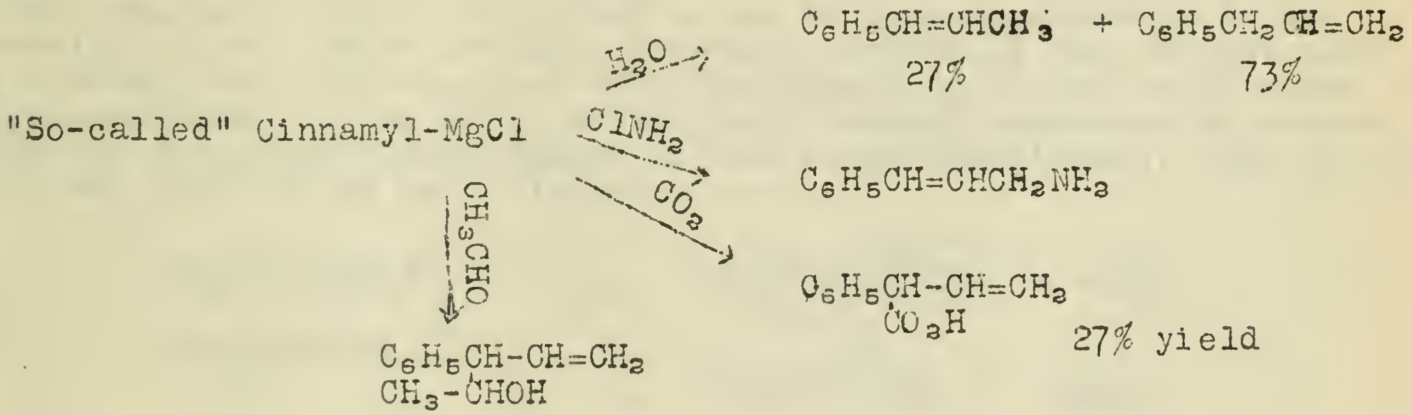
$$[RCH{=}CHCH_2{:}]^{\ominus}[MgX]^{\oplus} \longleftrightarrow [R\ddot{C}HCH{=}CH_2]^{\ominus}[MgX]^{\oplus}$$

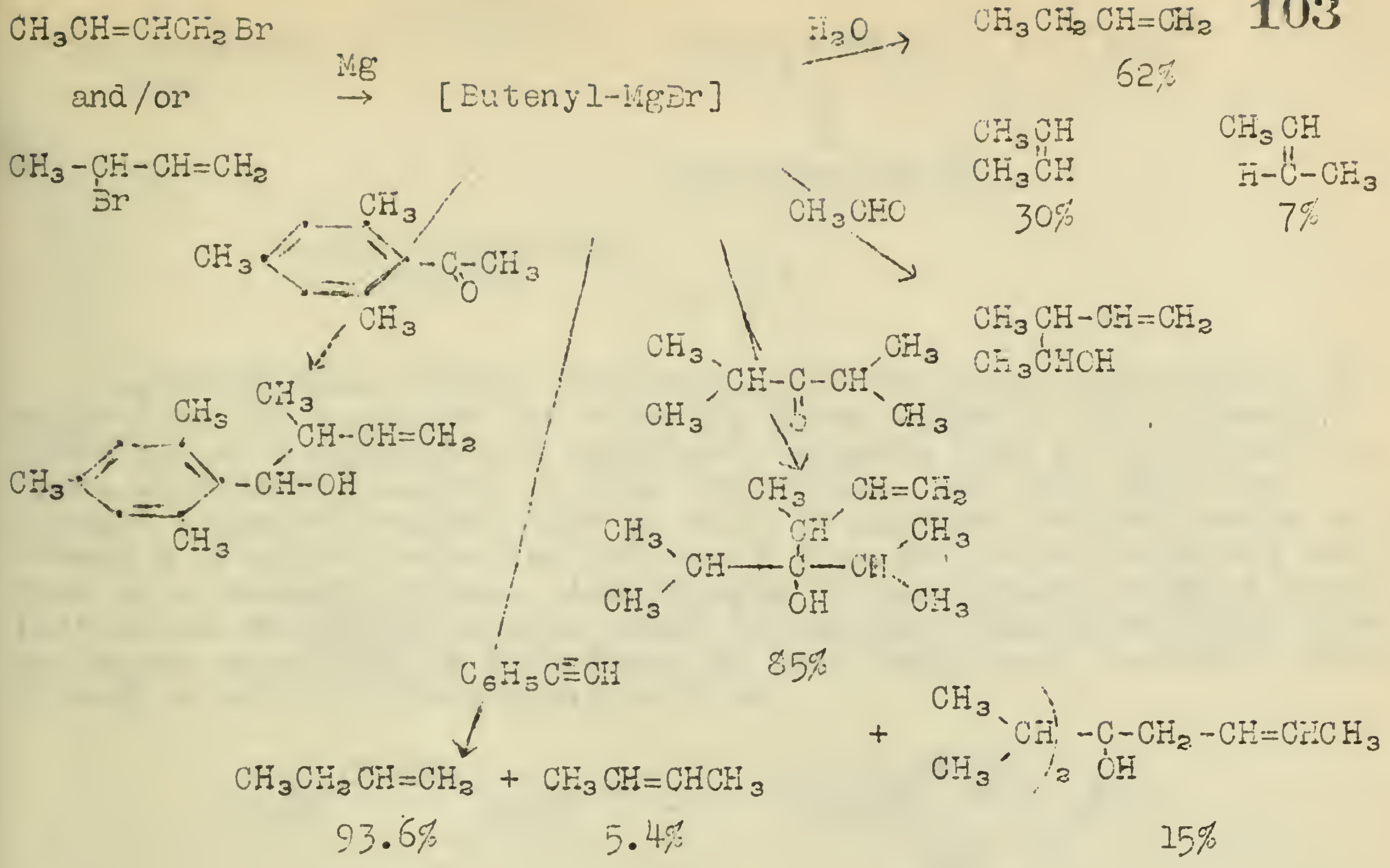
III

It is impossible to assign a structure to the reagent on the basis of the structure of starting materials or the products obtained from addition reactions with such a reagent until it has been determined whether

1.) Rearrangement occurs during the formation of the reagent.
2.) Equilibrium exists between I and II.
3.) Rearrangement occurs during addition.

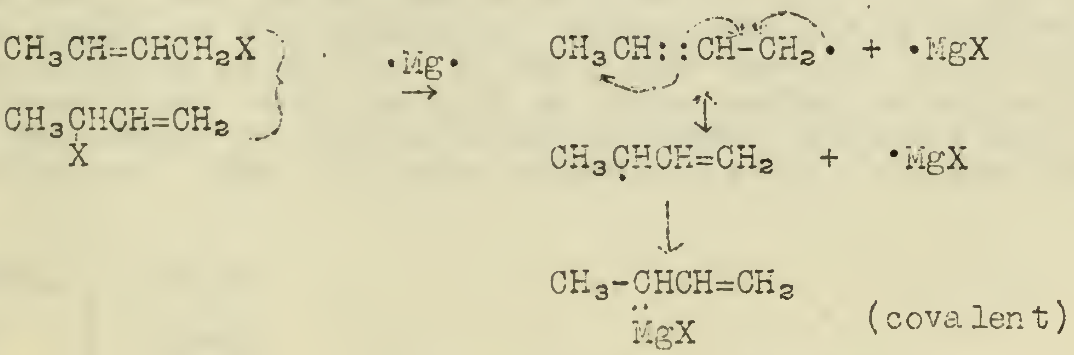
The experimental facts of the reactions of the phenylvinylcarbinyl-cinnamyl ("Cinnamyl") and the crotyl-methallyl ("Butenyl)" systems are outlined below.

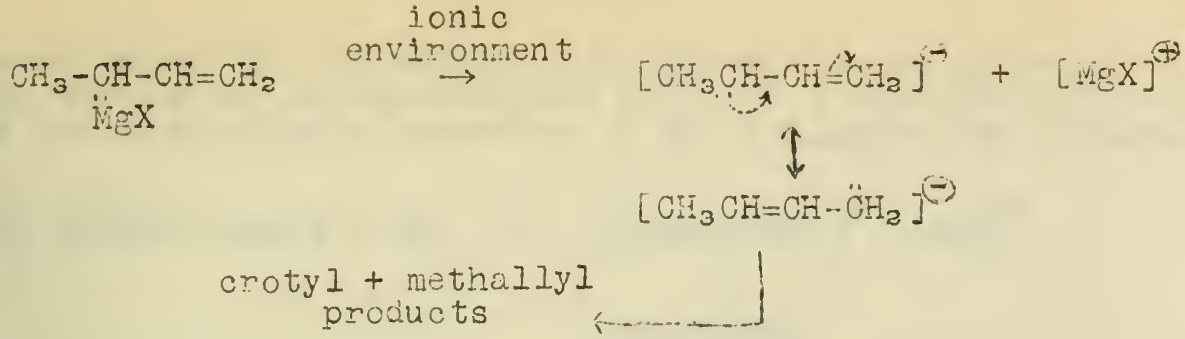

$C_6H_5CH{=}CHCH_3$ + $C_6H_5CH_2CH{=}CH_2$
27%
73%
H_2O
"So-called" Cinnamyl-MgCl
ClNH$_2$
$C_6H_5CH{=}CHCH_2NH_2$
CO_2
CH_3CHO
$C_6H_5CH(CO_2H){-}CH{=}CH_2$
27% yield
$C_6H_5CH{-}CH{=}CH_2$
$CH_3{-}CHOH$


CH₃CH=CHCH₂Br
and/or
CH₃-CH-CH=CH₂
Br
Mg
[Butenyl-MgBr]
H₂O
CH₃CH₂CH=CH₂
62%
CH₃CH
CH₃CH
30%
CH₃CH
H-C-CH₃
7%
CH₃CHO
CH₃CH-CH=CH₂
CH₃CHOH
CH₃
CH₃
-C-CH₃
O
CH₃
CH₃
CH-CH=CH₂
CH₃
-CH-OH
CH₃
CH₃
CH-C-CH
CH₃
CH₃
O
CH₃
CH₃
CH=CH₂
CH
CH₃
CH
C
CH
OH
CH₃
CH₃
CH₃
85%
C₆H₅C≡CH
CH₃CH₂CH=CH₂ + CH₃CH=CHCH₃
93.6%
5.4%
+
CH₃
CH
-C-CH₂-CH=CHCH₃
CH₃
2
OH
15%

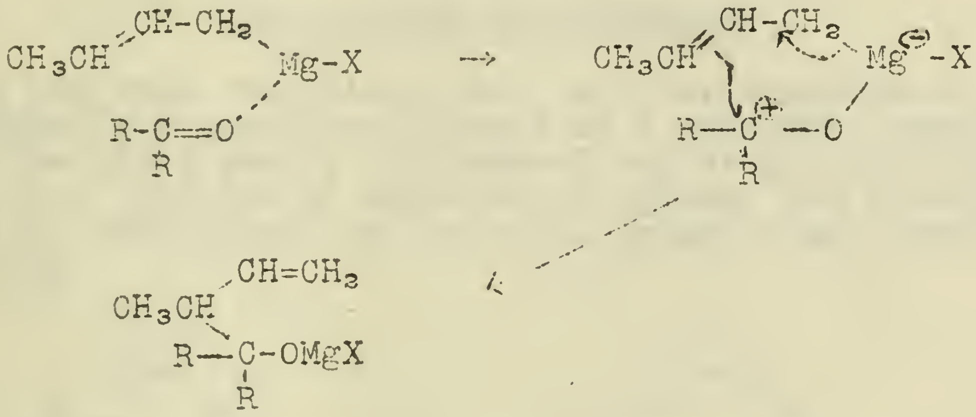
Only one product was isolated from each of the reactions above except in those cases where a mixture is indicated.

With the exception of the reaction with chloramine all of these data are consistent with the point of view that rearrangement occurs as the Grignard reagent is formed so as to be predominately in the methallyl form. Under ordinary Grignard conditions the reagent acts as a normal covalent compound with the resulting formation of methallyl products. In an ionic environment (water) dissociation occurs with the resulting establishment of the allyl equilibrium. The situation can be pictured as follows:

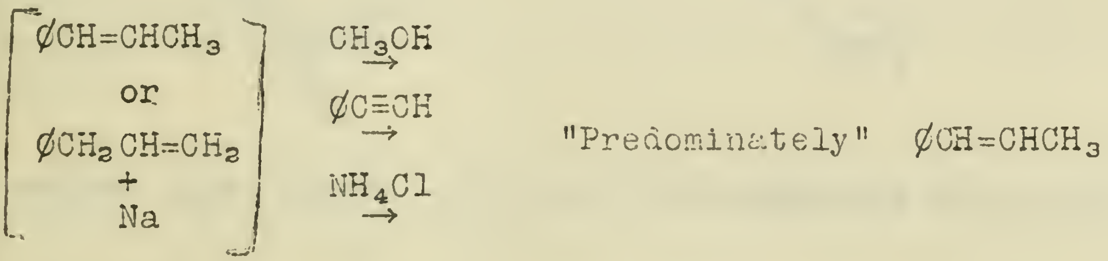

CH₃CH=CHCH₂X
CH₃CHCH=CH₂
X
·Mg·
CH₃CH::CH-CH₂· + ·MgX
CH₃CHCH=CH₂ + ·MgX
CH₃-CHCH=CH₂
MgX
(covalent)

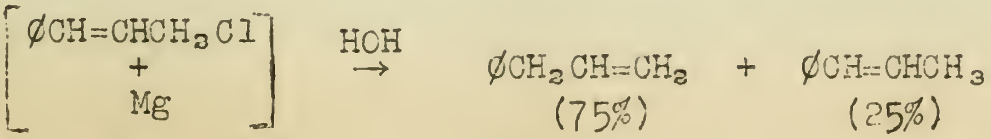

CH₃-CH-CH=CH₂
MgX
ionic environment
[CH₃CH-CH=CH₂]⊖
+
[MgX]⊕
[CH₃CH=CH-CH₂]⊖
crotyl + methallyl products

Although this scheme correlates moderately well the data with respect to the position the entering group takes in the molecule, there is one very striking fact that suggests that it is probably a gross oversimplification or even erroneous. The fact that the butenyl Grignard reagent adds so well to hindered ketones seems to demand a reaction mechanism different from the normal Grignard addition to a carbonyl group. Accordingly it is another point of view that it is the crotyl system which is the more stable covalent form and since magnesium is well known to form complexes, reaction occurs through a cyclic intermediate such as


CH₃CH
CH-CH₂
Mg-X
R-C==O
R
CH₃CH
CH-CH₂
Mg⊖-X
R—C⊕—O
R
CH₃CH
CH=CH₂
R—C-OMgX
R

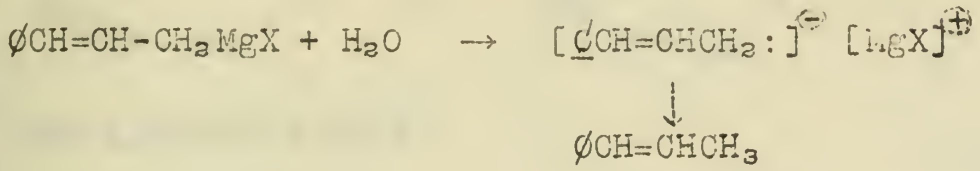
With respect to this mechanism the hydrolysis reactions of the cinnamyl Grignard reagent and sodium allyl benzene appear to have some bearing. Since sodium allyl benzene would not be expected to coordinate (e.g., as the magnesium derivative does with the carbonyl group) the nature of the hydrolytic medium should not influence the hydrolysis products obtained. On the other hand, if the cinnamyl Grignard reagent can react both by an ionic mechanism and a cyclic mechanism the nature of the hydrolyzing reagent should affect the products obtained. The following experiments verify these predictions:


ØCH=CHCH₃
or
ØCH₂CH=CH₂
+
Na
CH₃OH
ØC≡CH
NH₄Cl
"Predominately" ØCH=CHCH₃


ØCH=CHCH₂Cl
+
Mg
HOH
ØCH₂CH=CH₂
+
ØCH=CHCH₃
(75%)
(25%)

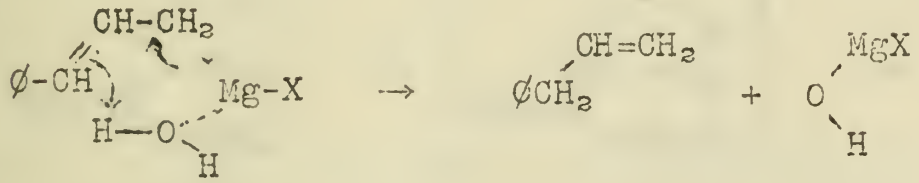
Accordingly, the formation of allylbenzene and propenylbenzene from the hydrolysis of the Grignard reagent is considered to be the result of the simultaneous operation of the following two mechanisms:

(A)



$$\phi CH{=}CH{-}CH_2MgX + H_2O \longrightarrow [\phi CH{=}CHCH_2:]^{\ominus}[MgX]^{\oplus} \xrightarrow{} \phi CH{=}CHCH_3$$

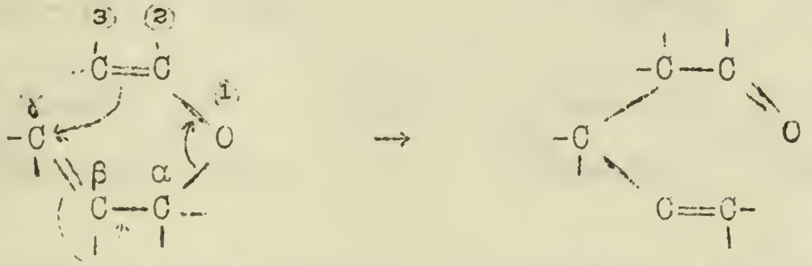
(B)



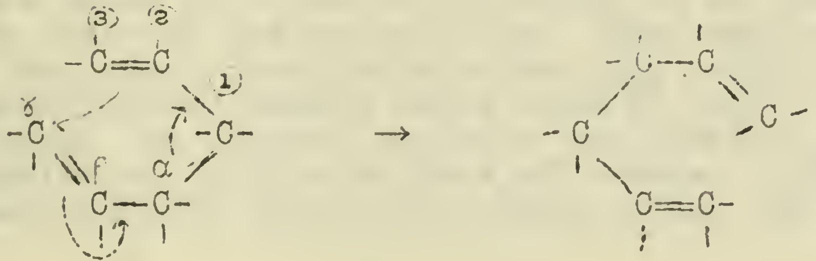
It is interesting that a consideration of the hyperconjugation forms and resonance with a benzene ring leads to the conclusion that the cinnamyl ion should be the more stable.

The Claisen Rearrangement

It is now well recognized that the rearrangement of allyl phenyl ethers is a specific instance of a much more general reaction involving the allyl group. In general any vinyl allyl ether (I) or biallyl system (II) may be expected to undergo the reaction provided that the β,γ double bond of the allyl group is not involved in an aromatic ring.



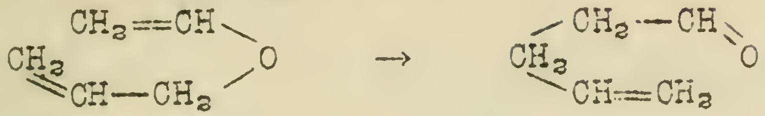
I



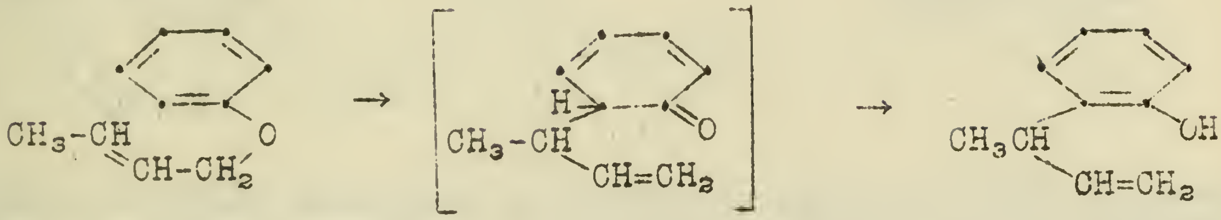
II

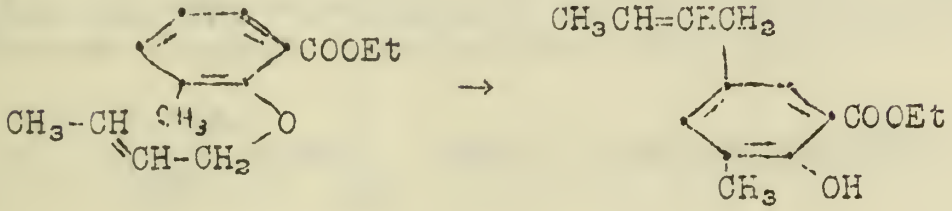
A rather large number of these rearrangements are known.

1.) Allyl vinyl ethers:

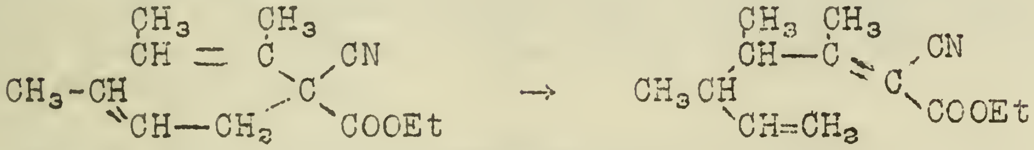


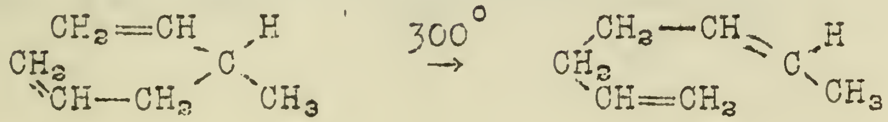
2.) Allyl phenyl ethers:





3.) Biallyl Systems:





Mechanism of the Reaction.--Almost all of the evidence concerning the Claisen rearrangement supports an intramolecular cyclic mechanism as shown in I and II, although it is difficult to see what the driving force of the reaction is. The reaction is first order (even when the allyl group enters the para position as in the case of o,o' disubstituted phenyl allyl ethers), and is not affected by acids or bases. No crossed products are obtained when the rearrangement is carried out with a mixture of ethers. Crotyl phenyl ether proceeds more rapidly than allyl phenyl ether but the reason is not clear.

When both ortho positions are occupied it will be observed that a similar reaction occurs in which the allyl group enters the para position, most frequently with no inversion of the allyl group. This is particularly significant taken with the fact that in one case at least the methallyl and the crotyl phenyl ethers both give the same product.

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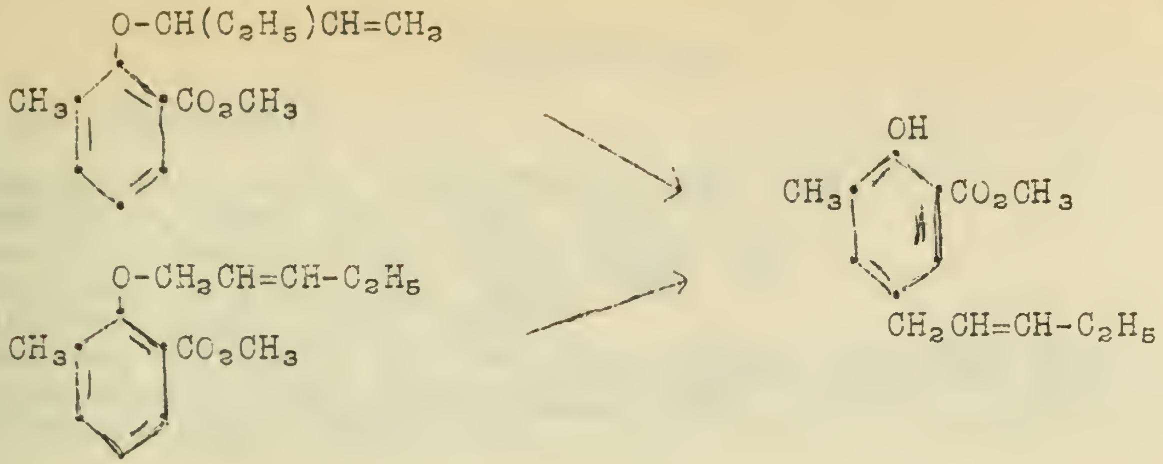
[illegible]

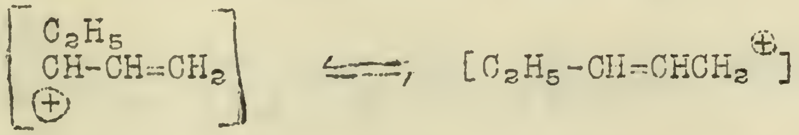
[illegible]

[illegible]

[illegible]



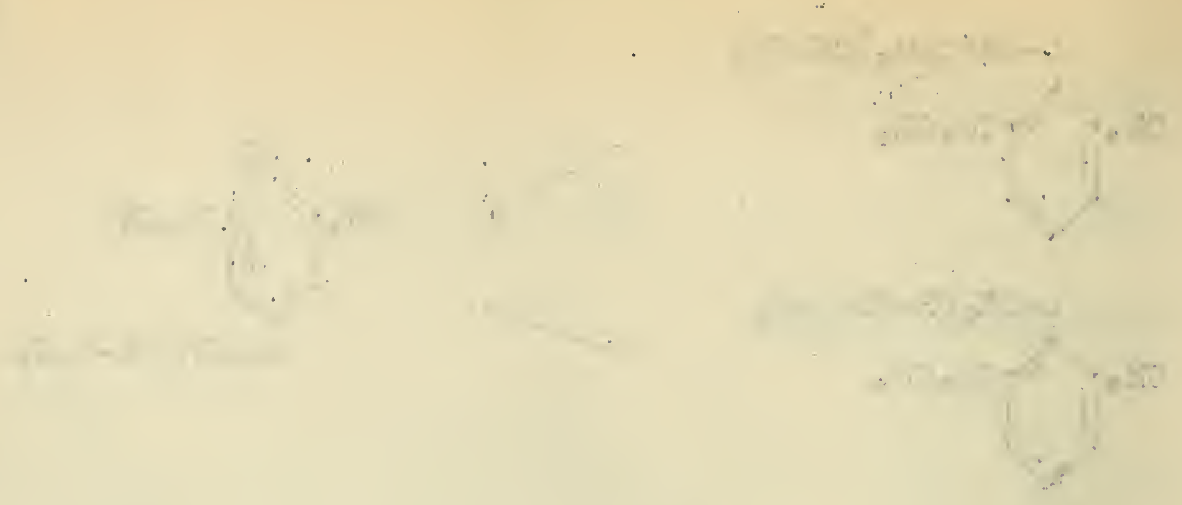
Certainly a cyclic mechanism is ruled out because of the distances involved, and the transient formation of radicals seems improbable since m substituted products are never obtained. The simplest explanation for this rearrangement is that the transformations both pass through a common intermediate state such as



$$\left[\begin{array}{l} C_2H_5 \\ CH-CH=CH_2 \\ \oplus \end{array}\right] \rightleftharpoons [C_2H_5-CH=CHCH_2^{\oplus}]$$

The obvious objection to the ionic mechanism, however, is that if allyl ions actually were free during the reaction, they should combine with a reactive solvent such as dimethyl aniline, and, as a result, lower the yield of rearrangement product. This is contrary to the observed facts.

As in the benzidine rearrangement no definite conclusion can be reached with regard to para rearrangement.



[illegible]

[illegible] of alkyl iron [illegible]

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α,β β,γ Equilibria

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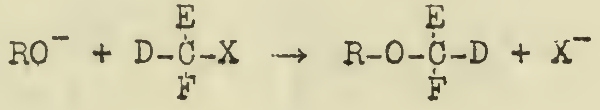
In the following discussion etherification will be considered to mean the formation of a carbon-oxygen-carbon linkage. Ether formation, in general, can be accomplished by two methods: base catalyzed or acid catalyzed.

Base Catalyzed Ether Formation.

The best known example of this type of reaction is the Williamson Synthesis. This reaction is a displacement reaction which normally proceeds by an S_N2 mechanism.

(1).



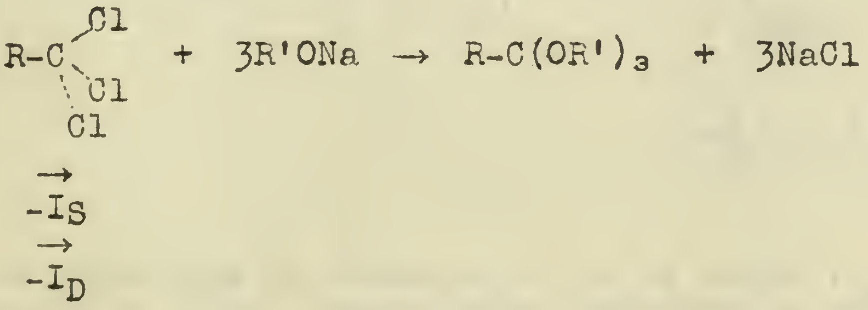
$$RO^- + D\text{-}\overset{E}{\underset{F}{C}}\text{-}X \rightarrow R\text{-}O\text{-}\overset{E}{\underset{F}{C}}\text{-}D + X^-$$

A B

B may be an alkyl halide, an alkyl toluenesulfonate or alkyl sulfate. A may be an alkoxide or phenoxide ion.

Woolf has shown that the reaction of various alkyl iodides with sodium eugenoxide in dry alcohol is essentially S_N2, but that the rate constant for a given iodide at a given temperature increased with dilution of the eugenoxide. This would be expected if the eugenoxide ion is the active agent since the degree of ionization increases with dilution. Hughes, Ingold, et. al. found that the reaction of ethyl or methyl alcohol with β-n-octyl bromide was predominantly S_N1, but, if the reaction medium was made approximately 1 N in KOH, the reaction was predominantly S_N2. Moreover, the reaction of the halide with sodium ethoxide in anhydrous ethanol was found to be almost 100% S_N2. Thus it appears that basic conditions, which lead to large concentrations of alkoxide or phenoxide ions, favor the S_N2 mechanism.

Orthoesters, which are really polyfunctional ethers, can also be formed by a base catalyzed Williamson reaction. The mechanism is the same as (1), a nucleophilic attack by R-O⁻ on the halide.



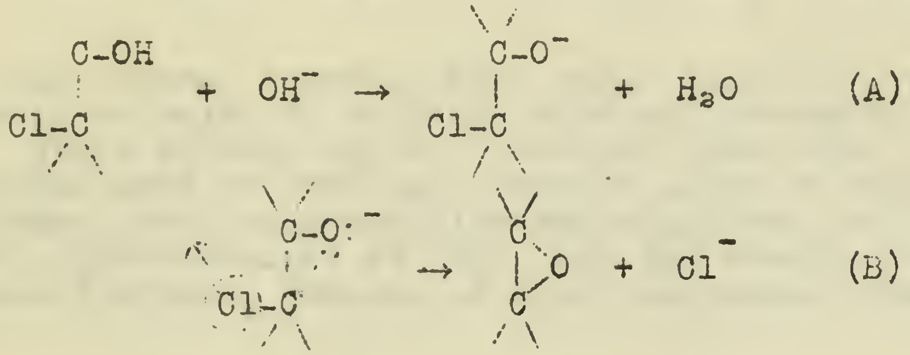
$$R\text{-}CCl_3 + 3R'ONa \rightarrow R\text{-}C(OR')_3 + 3NaCl$$

The ease of formation of the orthoester is enhanced by the combined

inductive (I_S) effect and inductomeric (I_D) effect of the three chlorine atoms.

Another example of base catalyzed etherification is the formation of epoxides by the action of alkali on α-chlorohydrins. The mechanism may be outlined as follows.

(2).

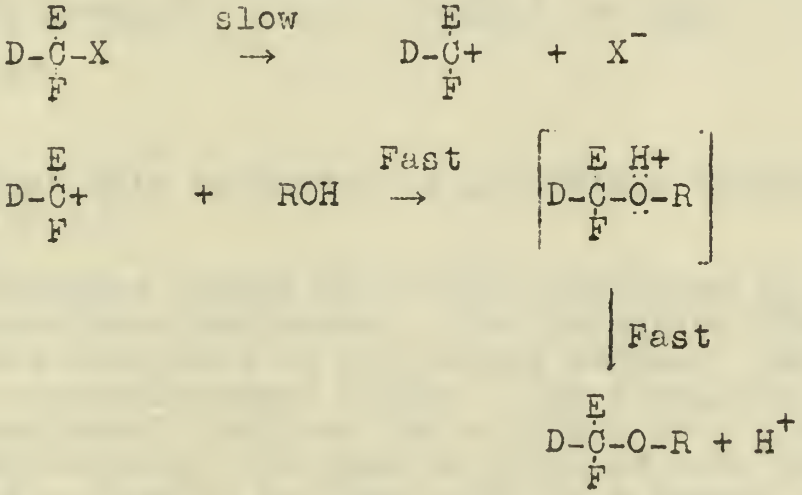


It is interesting to note that step (B) involves an intramolecular nucleophilic (S_N2) displacement. This particular displacement is extremely rapid due to the proximity of the reacting groups in the intermediate alkoxide ion.

Acid Catalyzed Ether Formation.

Although the Williamson Synthesis is carried out under basic conditions, certain alkyl halides will react with alcohols in the absence of bases to give ethers as products, hydrogen halide being formed in the process. Under these conditions the mechanism is presumably S_N1.

(3).



$$D\text{-}\overset{E}{\underset{F}{C}}\text{-}X \xrightarrow{\text{slow}} D\text{-}\overset{E}{\underset{F}{C}}+ \; + \; X^-$$

$$D\text{-}\overset{E}{\underset{F}{C}}+ \; + \; ROH \xrightarrow{\text{Fast}} \left[D\text{-}\overset{E}{\underset{F}{C}}\text{-}\overset{H+}{\ddot{O}}\text{-}R \right] \xrightarrow{\text{Fast}} D\text{-}\overset{E}{\underset{F}{C}}\text{-}O\text{-}R + H^+$$

An example of this type of reaction is to be found in the case of the etherification of dl α-phenylethyl chloride in ethanol. The rate of this reaction is independent of the concentration of ethoxide ion used.

The mechanism which was proposed by Williamson for the intermolecular dehydration of alcohols by sulfuric acid was based upon the intermediate formation of an alkyl sulfonic ester.

$$C_2H_5OH + H_2SO_4 \rightleftharpoons C_2H_5\text{-}O\text{-}SO_3H + H_2O$$

$$C_2H_5\text{-}OSO_3H + C_2H_5OH \rightleftharpoons C_2H_5\text{-}O\text{-}C_2H_5 + H_2SO_4$$

Van Alphen and others, however, have shown that the postulation of the half ester or ester of sulfuric acid as intermediates is not necessary. Ethyl alcohol may be converted into ether by heating it with any strong acid or even with certain salts of weak organic or inorganic bases, such as morpholine hydrochloride and ferric sulfate. HCl is also a good catalyst at 155°, but the reaction cannot proceed by Williamson's scheme, because at this temperature ethyl chloride

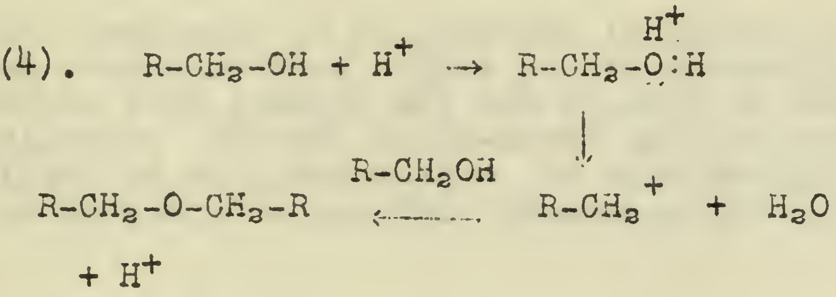
$$EtOH + HCl \rightarrow EtCl + H_2O$$

$$EtCl + EtOH \rightarrow Et\text{-}O\text{-}Et + HCl$$

does not react with alcohol.

The following mechanism may be postulated for the reaction.

(4).



$$R\text{-}CH_2\text{-}OH + H^+ \rightarrow R\text{-}CH_2\text{-}\overset{H^+}{\ddot{O}}\text{:}H$$

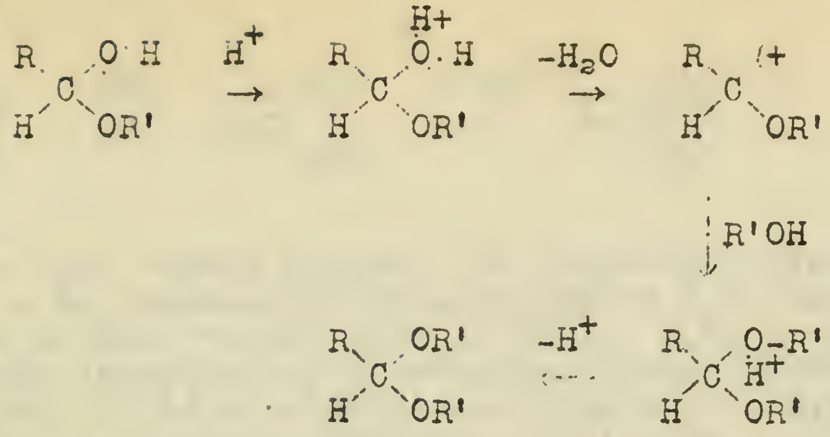
$$\downarrow$$

$$R\text{-}CH_2\text{-}O\text{-}CH_2\text{-}R + H^+ \xleftarrow{R\text{-}CH_2OH} R\text{-}CH_2^+ + H_2O$$

It will be noted that this mechanism is an obvious extension of the general S_N1 reaction (3).

Acetals are diethers formed by an acid catalyzed S_N1 addition of ROH to the intermediate hemiacetal. The mechanism for hemiacetal formation was described in a previous seminar, "Addition to Carbon-Oxygen and Carbon-Nitrogen Bonds". The formation of the acetal from the hemiacetal involves the addition of a proton followed by the dissociation of the oxonium compound into water and a carbonium ion. The carbonium ion then adds to a second molecule of alcohol to give the conjugate base of the acetal. These reactions are illustrated in (5).

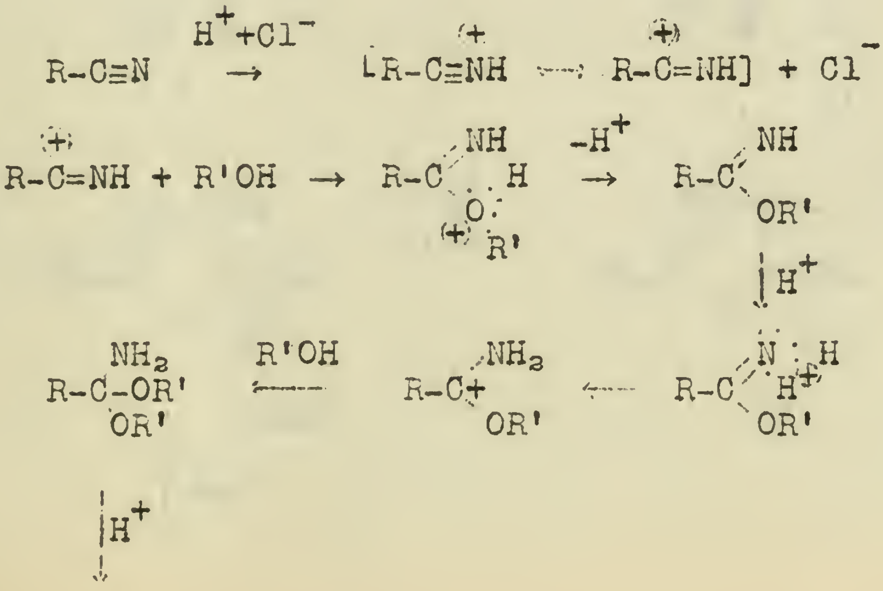
(5).

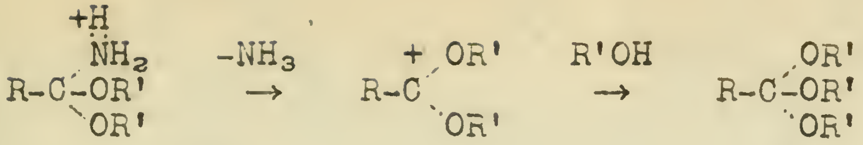


Experimentally it is known that it is easier to form an acetal from a hemiacetal than to form an ordinary ether. This is in accord with theory since the + E effect of the -OR' group of the hemiacetal enhances the stability of the intermediate carbonium ion and thus increases the ease of formation of the second C-O-C bond.

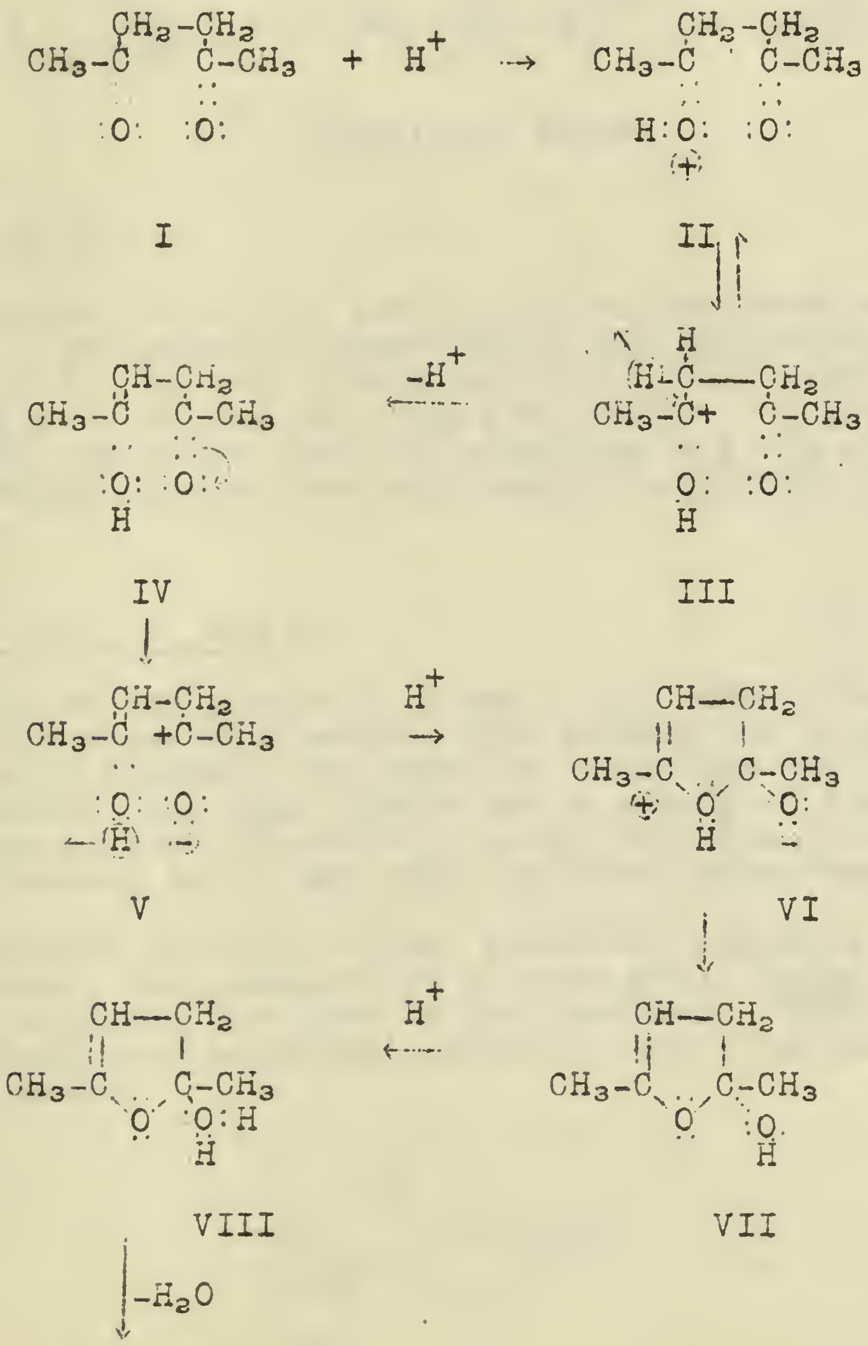
Quantitative studies of acetal formation have shown that the order of reactivity for the alcoholic component is: primary > secondary > tertiary. The primary alcohol is more reactive since it is less likely to form a carbonium ion than either the secondary or tertiary alcohol. From mechanism (5) it can be seen that the alcohol, R'OH, adds to the carbonium ion formed from the hemiacetal. Therefore, the alcohol which will add the most readily will be that one (the primary alcohol) which has the least tendency to form a carbonium ion.

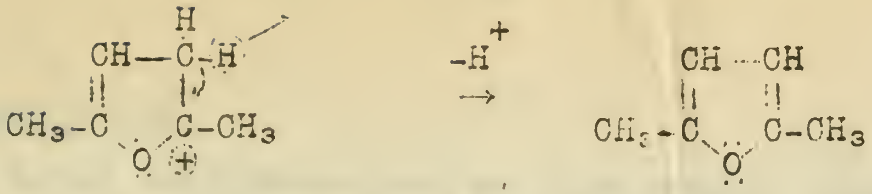
The Pinner Synthesis of orthoesters is another example of an acid catalyzed etherification. This reaction consists in the treatment of a nitrile with gaseous HCl and alcohol to form an imino-ester hydrochloride. The dry imino-ester hydrochloride, which is actually isolated as an intermediate, is then treated with alcohol to give the orthoester. A possible mechanism for this reaction is as follows.




+H
NH₂
R-C-OR'
OR'
-NH₃
+ OR'
R-C
OR'
R'OH
OR'
R-C-OR'
OR'

One of the most common methods for preparing five-membered cyclic ethers is by dehydration of appropriate 1,4-diketones or aldehydes by an acidic reagent such as $ZnCl_2$, P_2O_5 or H_2SO_4. The mechanism for the formation of 2,5-dimethylfuran illustrates this type of reaction. It is a particularly interesting type of etherification in that it probably involves addition to a carbonyl group (V-VI) followed by an elimination reaction (VII-X).

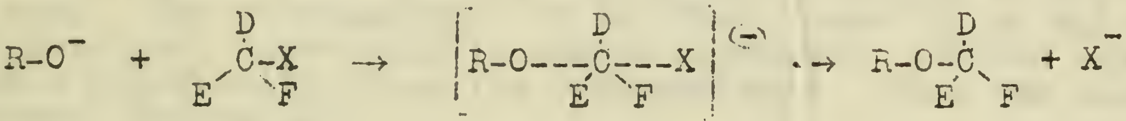

I
II
III
IV
V
VI
VII
VIII
+ H+
-H+
H+
H+
-H₂O



IX X

Factors Affecting the Ease of Formation of Ethers.

In the generalized S_N2 mechanism the ease of ether formation will depend on three factors: the nature of X, the nature of D, E and F, and the nature of $R\text{-}O^-$.



Transition State

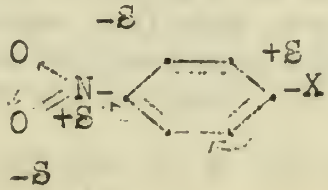
1. The Nature of X.

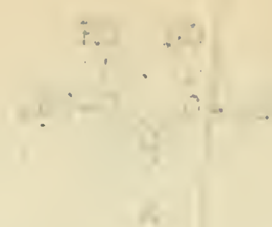
The $-I_S$ effect of X will facilitate the approach of ^-OR and the removal of X^-. The order of magnitude of the $-I_S$ effect for the halogens is Cl > Br > I. The $-I_D$ effect will also facilitate the removal of X^-. In the case of the $-I_D$ effect the order for the halogens is I > Br > Cl. The $-I_D$ effect usually outweighs the $-I_S$ effect, and consequently alkyl iodides are more easily etherified than bromides and chlorides.

2. The Nature of D, E, and F.

The nature of the groups D, E and F will affect the ease of formation of the transition state. The feeding in of electrons by alkyl groups will increase the negative charge on the C atom involved in the displacement and thus hinder the approach of $R\text{-}O^-$. For this reason the ease of etherification of alkyl halides by the S_N2 mechanism in general is in the order primary > secondary > tertiary.

Etherification of aryl halides generally requires vigorous conditions. However, the presence of a nitro group *ortho* or *para* to the halogen atom increases the ease of the reaction. This is presumably due to the creation of a partial positive charge on the atom at which displacement occurs.



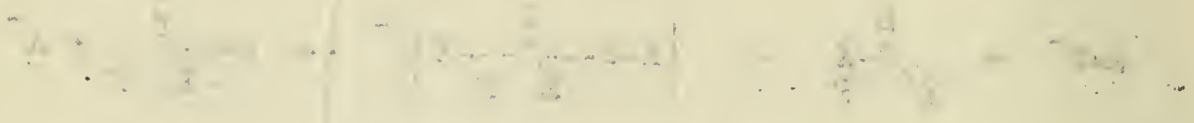


A

II

Factors Influencing the Rate of Formation of Ethers.

In the expressions for the rate of ether formation we will attempt to discuss the nature of X, the nature of R, R' and R'', and the nature of RO⁻.



Transition State

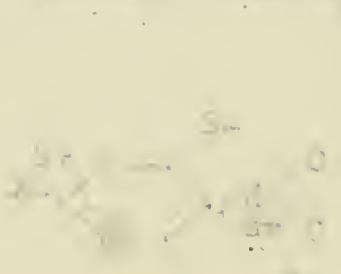
1. The Nature of X.

The [illegible] effect of X which facilitates the departure of X⁻ and the approach of [illegible]. The order of [illegible] of [illegible] I > Br > Cl. [illegible] in the case of [illegible] effect [illegible] and [illegible] and chlorides.

2. The Nature of R, R' and R''.

The nature of the groups R, R' and R'' [illegible] the ease of separation of the [illegible]. The [illegible] of [illegible] the [illegible] and the [illegible] is the displacement and thus [illegible]. For this reason the ease of [illegible] of [illegible] in the order [illegible].

Etherification of [illegible] alcohols [illegible]. However, the presence of a [illegible] group [illegible] the ease of the [illegible] to the [illegible] of a partial [illegible] on the [illegible] of the displacement centre.



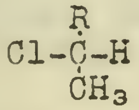
3. The Nature of RO^-.

It is known that phenoxides are more easily etherified than alkoxides. Just why this is true is not known definitely. It may be due to the fact that the phenoxides are more highly ionized than alkoxides, and hence the phenoxide ions are present in higher concentration.

Stereochemistry of Ether Formation.

It has been well established that the S_N2 etherification reaction involves the inversion of configuration around an asymmetric carbon atom. The configuration of an ether formed by an S_N1 mechanism is uncertain, especially if plural asymmetric centers exist or there is a possibility of cyclic intermediates. (See the seminar on Displacement Reactions).

The situation may be summarized by a table showing the results obtained by Hughes, Ingold, et. al., who studied the hydrolysis and alcoholysis of certain alkyl halides.

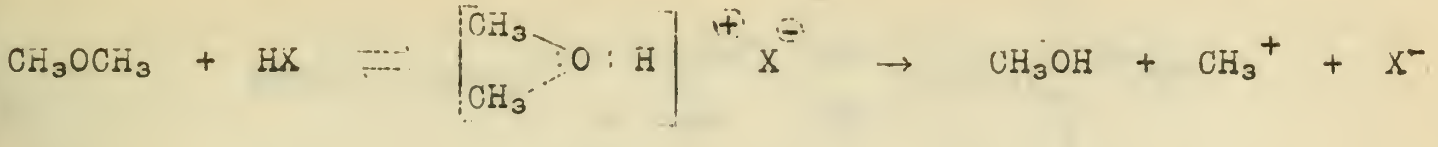
R  $\mathrm{Cl-\overset{R}{\underset{CH_3}{C}}-H}$	Effect on Configuration	
	S_N2 Mechanism	S_N1 Mechanism
C_6H_{13} (n-hexyl)	Inversion	Racemization and inversion
$C_6H_5^-$	"	Large Racemization and Inversion
-COOH or -COOMe	"	Not known
$-COO^-$	"	Retention

In certain cases retention of configuration may be the result of successive displacements.

Acid Catalyzed Cleavage of Ethers.

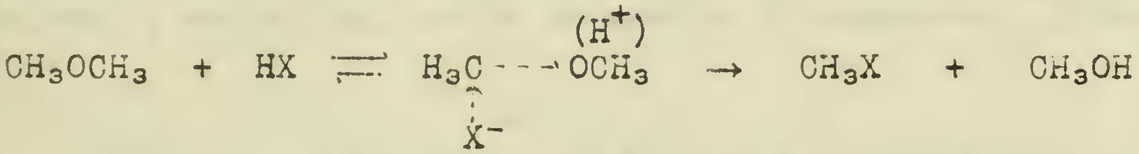
Acidic reagents, particularly the hydrogen halides, have been the most widely used in the cleavage of ethers. Ratios of the effectiveness of the hydrogen halides are HCl:HBr:HI = 1:6:[illegible]. With strong mineral acid at low temperature ethers form oxonium salts. This suggests two possible mechanisms for the cleavage of ethers:

1. An electrophilic attack by H^+ on oxygen followed by decomposition of the oxonium salt.



$$CH_3OCH_3 + HX \rightleftharpoons \left[\begin{matrix} CH_3 \\ CH_3 \end{matrix} \!\!> O:H \right]^{+} X^{-} \rightarrow CH_3OH + CH_3^{+} + X^{-}$$

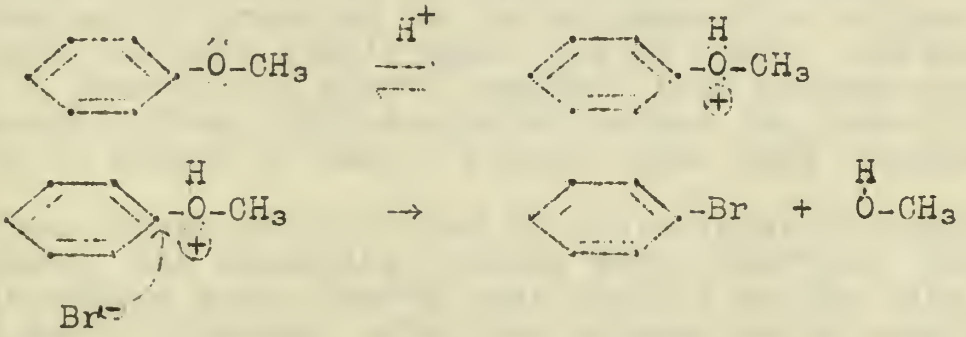
2. A nucleophilic attack by X^- on C which may or may not be preceded by oxonium salt formation.



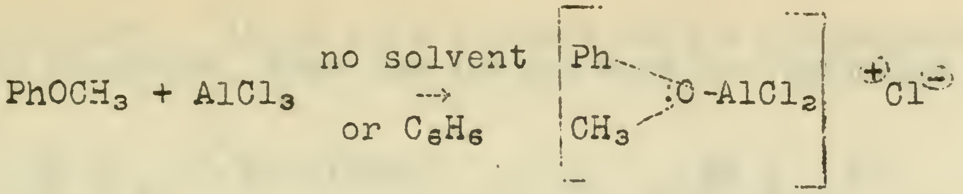
$$CH_3OCH_3 + HX \rightleftharpoons \underset{X^-}{H_3C} \cdots \overset{(H^+)}{OCH_3} \rightarrow CH_3X + CH_3OH$$

Birosel determined that in the presence of excess HBr in acetic and formic acids the reaction was first order for 2,4-dibromophenyl methyl ether while a number of napthol ethers were also found to be cleaved by a first order reaction when a large excess of HBr in glacial acetic acid was used. Ghaswalla and Donnan cleaved anisole and phenetole as well as the substituted derivatives by excess HCl and HBr and found the reaction to be first order. This is in agreement with the assumption that oxonium salt formation occurs as an intermediary step followed by decomposition of the oxonium salt. It is the decomposition of this intermediate which is the rate determinin step.

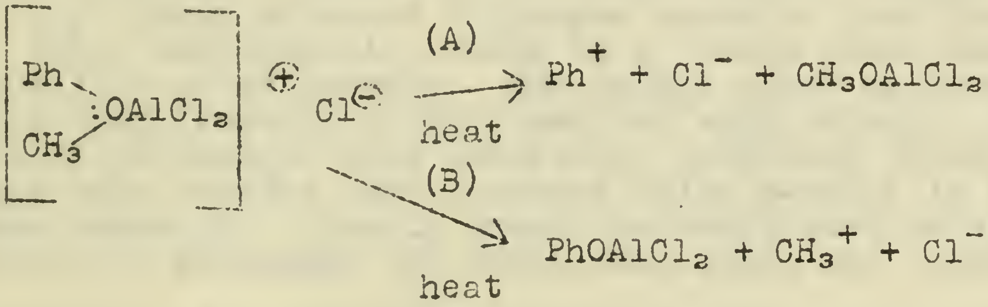
That a pure first order decomposition of the oxonium ion does not occur is clear from the observation that various substituted anisoles were not cleaved by HCl or HBr under the usual conditions if the reaction was carried out in n-hexane or CCl_4. The effect of adding a small amount of base such as pyridine, dimethylaniline, or aniline was very striking as fission then occurred readily. Also the presence of one of the above mentioned bases will increase the rate of cleavage of ethers by HX in acetic acid solution. These factors imply, at least in this case, that the reaction should be written



Other electrophilic reagents capable of forming oxonium salts with ethers have been used frequently in cleavage, especially of Aralkyl ethers. Some of these are $AlCl_3$, $AlBr_3$, $ZnCl_2$, $FeCl_3$, $SnCl_4$, $SbCl_5$, and BF_3. For anisole and aluminum chloride the following mechanism could be postulated.



This complex could conceivably decompose in two ways upon heating depending upon whether the phenyl-oxygen or the methyl-oxygen bond was broken. However, the first mechanism (A) cannot take place because a phenyl carbonium ion is incapable of existence. Treatment



of $PhOAlCl_2$ with water will give the phenol.

A study of reaction rates for the cleavage of three alkyl ethers by strong acids shows the following.

	K
Diethyl ether	2.43×10^{-13}
Ethyl isopropyl ether	2.50×10^{-12}
Di-isopropyl ether	1.10×10^{-11}

This would be expected from the first mechanism proposed since electro release would be more pronounced in the isopropyl radical ($+I_D$ effect) and hence an increased density of electrons would occur on the ether oxygen promoting attack by an electrophilic reagent. Also the isopropyl carbonium ion produced by the decomposition of the oxonium intermediate would be more stable than that of ethyl, and more likely to form due to a greater $+I_D$ effect together with greater hyperconjugation possibilities. For a similar reason the rate of cleavage of phenetole by an excess of HBr is greater than that of anisole.

When various ethers were cleaved by equimolecular quantities of HBr in acetic acid, the following results were observed. The aromatic-aliphatic ethers were cleaved less readily as the alkyl chain was lengthened and di-*n*-propyl ether was attacked more readily than di-isopropyl ether. This trend is exactly the opposite from what would be expected if the reaction proceeded by the intermediate formation of the oxonium ion followed by its first order decomposition. However, the cleavage of ethers proceeds by a first order mechanism only when the halogen acid is present in considerable excess. With equivalent quantities of halogen acid and ether evidence has been advanced to show that second order and third order reactions

[illegible]

[illegible]

This [illegible]

(A) [illegible]

(B) [illegible]

[illegible] with other data (21) [illegible]

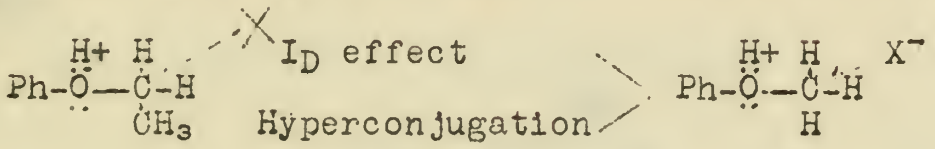
As a result of [illegible]

Diethyl ether	[illegible]
Ethyl isopropyl ether	[illegible]
Di-isopropyl ether	[illegible]

This would be expected [illegible]

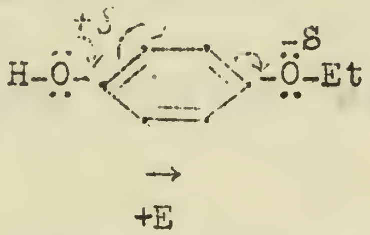
[illegible]

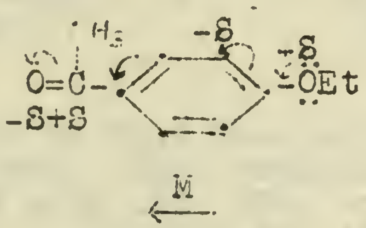
may be in operation. If it were assumed that a nucleophilic attack by X^- on C be involved, then the facts could be explained.



The $+I_D$ effect for a group like *n*-propyl would be less than for a group like isopropyl, hence the electron density around the C atom of the *n*-propyl group attached to oxygen would be less than that for isopropyl, and a nucleophilic attack by X^- could occur more readily. Certain anomalies occur however. The methyl ether of β-napthol is more readily hydrolyzed by 5N HCl than the ethyl ether. With equivalent amounts of halogen acid and ether, isopropyl phenyl ether is cleaved much more rapidly than *n*-propyl while *n*-butyl is cleaved more readily than isobutyl. Clearly these reactions must be studied in greater detail to determine the mechanisms which are involved.

The presence of nuclear substituents have a marked effect upon the cleavage of Aralkyl and diaryl ethers. Substituted anisoles are split by HX with an ease indicated by the following series: $CH_3O > CH_3 > OH > Cl > Br$. The ease of cleavage also varies with the position of the substituent in the order *p* > *o* > *m*. In the case of *m*-directing substituents the order is acetyl > nitro and in each case the order of the isomers is reversed, *m* > *o* > *p*.

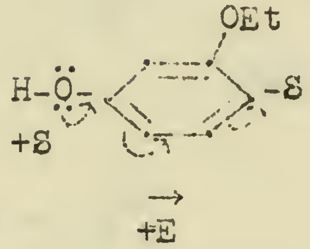




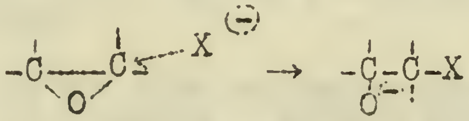
For substituted napthol ethers the relative effect of substituents was Me > Br > Cl > NO_2. Birosel determined that increasing the substitution by halogen in phenetoles decreased the amount of decomposition.

Electrophilic attack by H^+ occurs more readily on the ethereal oxygen when a greater density of electrons is present which would be the case when an electron donating group such as -OH is present in the ring in an *ortho* or *para* position. When the group is present

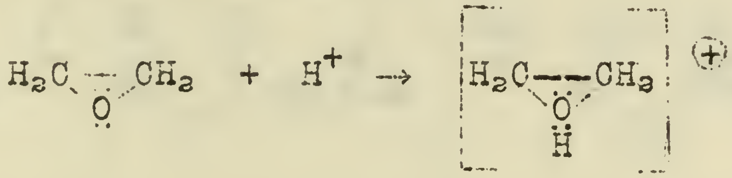
in the meta position, the same donating occurs; however, since the ethereal linkage is now at the meta position, a much smaller effect is observed.



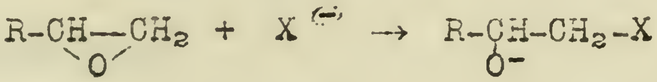
In general alkaline or neutral cleavage of epoxides is the result of a nucleophilic attack on one of the carbons attached to oxygen.


$$\underset{\mathrm{O}}{\mathrm{-C{-}C}} \cdots \mathrm{X}^{\ominus} \rightarrow \mathrm{-}\underset{\mathrm{O^-}}{\mathrm{C}}\mathrm{{-}C{-}X}$$

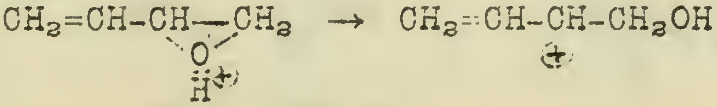
Acids accelerate the cleavage by the formation of an oxonium intermediate in which the C-O bond is weakened.


$$\underset{\ddot{\mathrm{O}}}{\mathrm{H_2C{-}CH_2}} + \mathrm{H^+} \rightarrow \left[\underset{\underset{\mathrm{H}}{\ddot{\mathrm{O}}}}{\mathrm{H_2C{-}CH_2}}\right]^{\oplus}$$

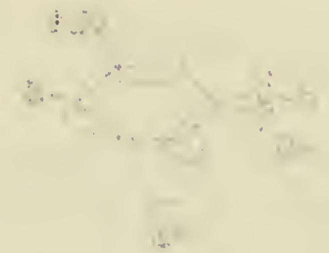
In the case of unsymmetrical epoxides the least substituted carbon atom, i.e. the one which possesses the lowest electron density has its C-O bond broken.


$$\underset{\mathrm{O}}{\mathrm{R{-}CH{-}CH_2}} + \mathrm{X}^{\ominus} \rightarrow \mathrm{R{-}}\underset{\mathrm{O^-}}{\mathrm{CH}}\mathrm{{-}CH_2{-}X}$$

One of the exceptions to this rule is the compound in which R is vinyl, 3,4-epoxy-1-butene. This compound undergoes an "abnormal" ring opening when treated with HCl, HBr, or acidic methanol. This "abnormal" reaction may be accounted for if we consider that a unimolecular ring opening occurs in the acid catalyzed reaction as follows.

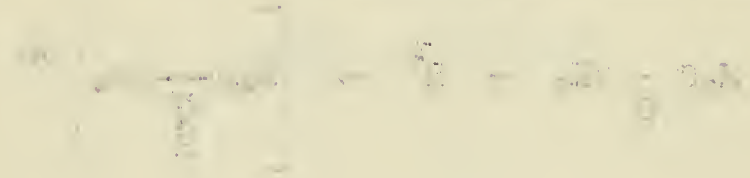

$$\mathrm{CH_2{=}CH{-}}\underset{\underset{\mathrm{H^{\oplus}}}{\mathrm{O}}}{\mathrm{CH{-}CH_2}} \rightarrow \mathrm{CH_2{=}CH{-}}\underset{\oplus}{\mathrm{CH}}\mathrm{{-}CH_2OH}$$

In the para position, the same reaction occurs; however, since the inserted [illegible] is not at the para position, a more complex effect is observed.



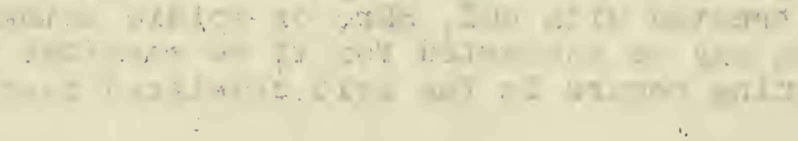
In general alkaline or neutral cleavage of epoxides is the result of a nucleophilic attack on one of the epoxide carbons to oxygen.

Acids accelerate the cleavage by the formation of a cyclic intermediate in which the C-O bond is weakened.

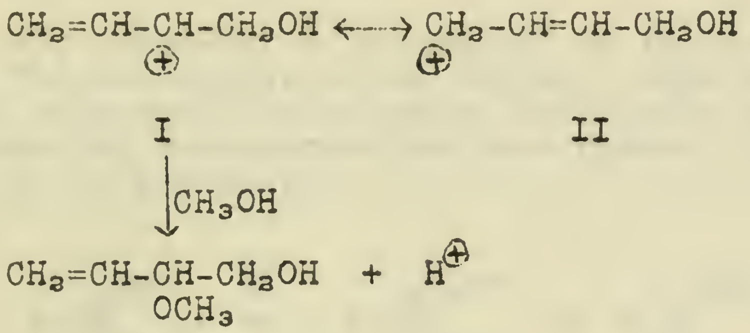


In the case of unsymmetrical epoxides the least substituted carbon atom, i.e., the one which possesses the lowest electron density, has its C-O bond broken.

One of the exceptions to this rule is the compound in [illegible] 1,2-epoxy-1-butene. This compound undergoes an "abnormal" ring opening when treated with HCl, HBr, or acetic anhydride. This "abnormal" reaction may be accounted for if we consider that a [illegible] molecular ring opening occurs in the acid catalyzed reaction as follows.



The carbonium ion formed is stabilized by the resonance forms I and II.

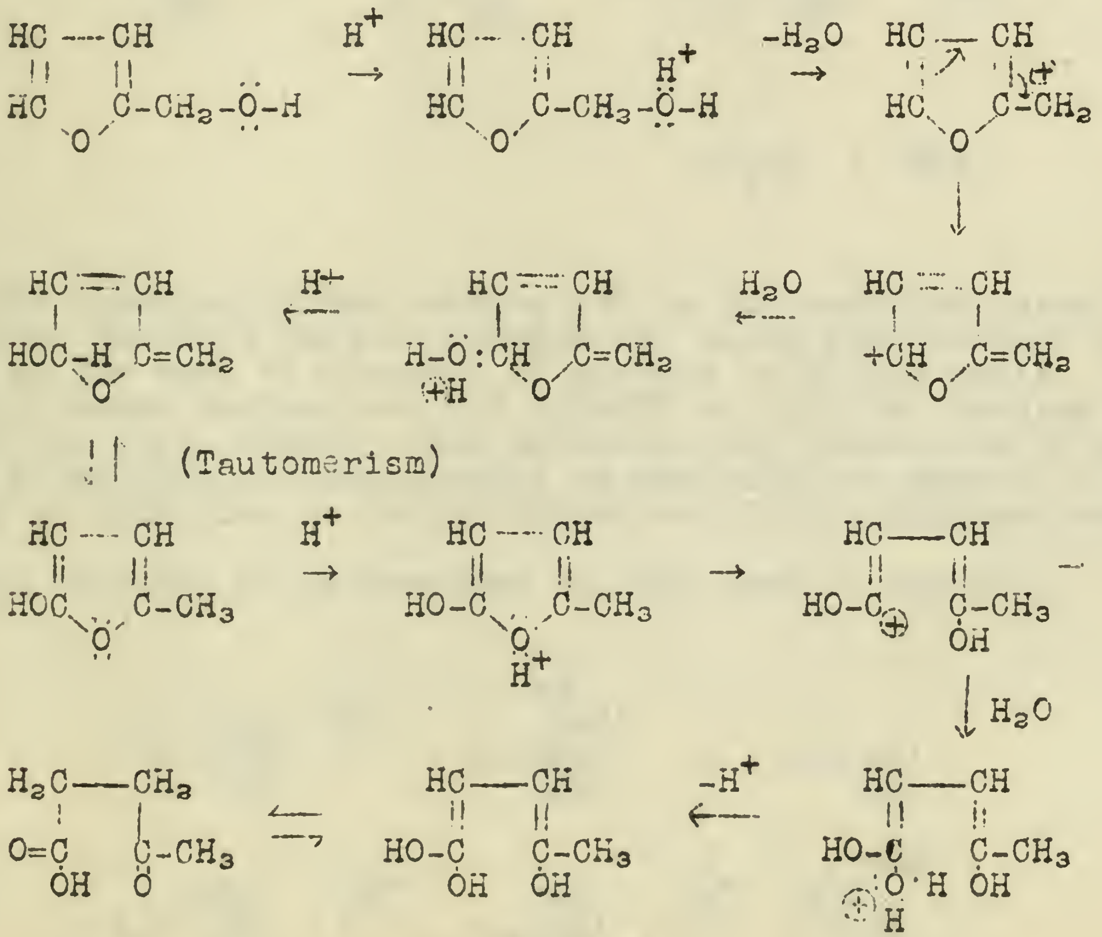


$$\underset{\text{I}}{CH_2{=}CH{-}\overset{}{\underset{\oplus}{CH}}{-}CH_2OH} \longleftrightarrow \underset{\text{II}}{\underset{\oplus}{CH_2}{-}CH{=}CH{-}CH_2OH}$$

$$\xrightarrow{CH_3OH} CH_2{=}CH{-}\underset{OCH_3}{CH}{-}CH_2OH + H^{\oplus}$$

It seems likely that other acid catalyzed ring openings of styrene oxide, isobutylene oxide, and 3,4-epoxy-1-butene derivatives which proceed "abnormally" also involve unimolecular opening and a carbonium ion intermediate.

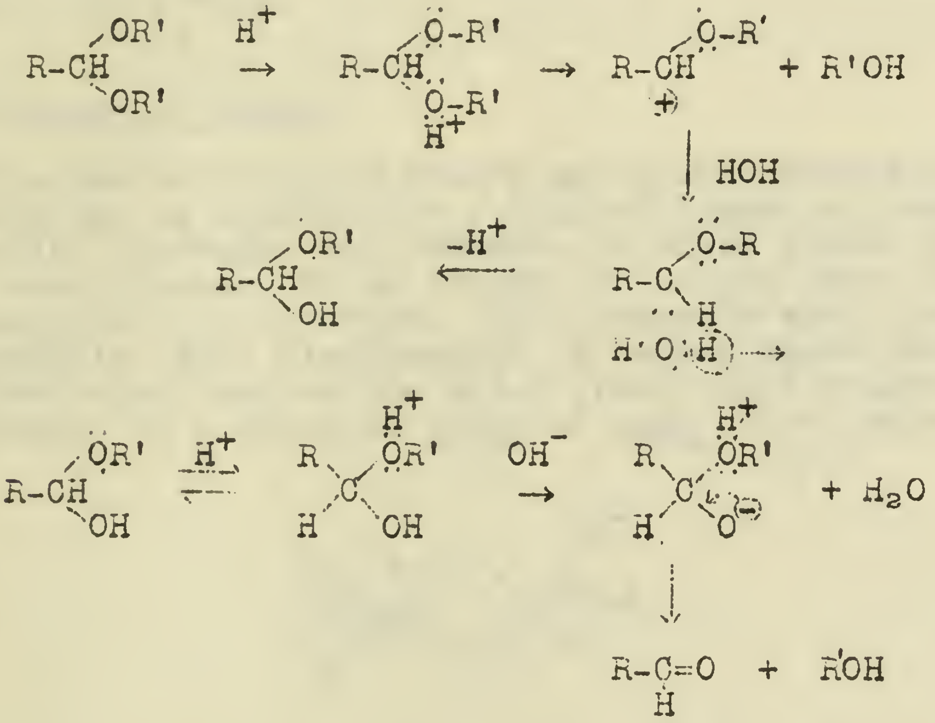
The usual ether cleavage with halogen acids is also applicable to the five-membered cyclic ethers. Dilute HCl in methanol will cause furfuryl alcohol to yield levulinic acid. A possible mechanism for this reaction is the following.



enol form of levulinic acid

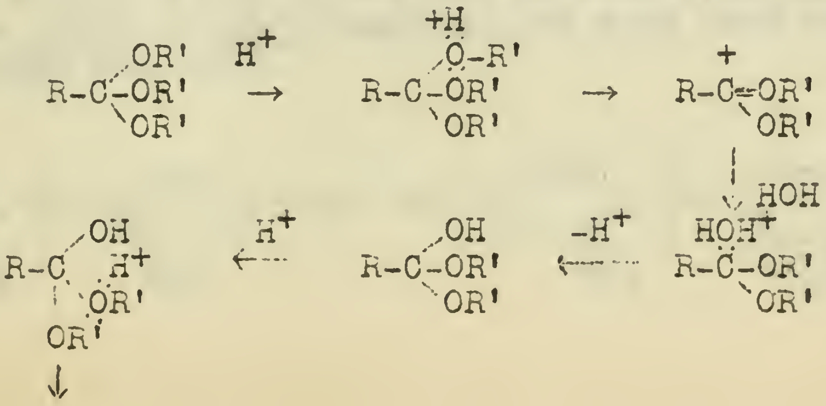
As previously described for the ROR type ethers, the essential cleavage step in this reaction is the formation of the oxonium ion and the cleavage of this ion.

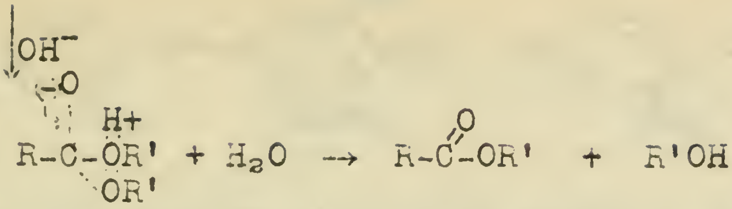
As in its formation a hemiacetal is the most probable intermediate in the hydrolysis of an acetal. This has been shown to be true in the cleavage of the acetal linkage in sucrose where the stable hemiacetal monosaccharides are formed. The steps in the hydrolysis of an acetal are --



Again the cleavage of the oxonium ion is the essential step of the reaction. The fact that an oxonium ion is an intermediate is supported by the ease of cleavage of acetals in acidic media. In basic solution, where protons are not present to form the oxonium ions, acetals are quite stable. The mechanism for conversion of an hemiacetal to an aldehyde and alcohol is described on page 4 of the seminar on "Addition to Carbon-Oxygen and Carbon-Nitrogen Bonds".

The cleavage of orthoesters is like that of acetals.



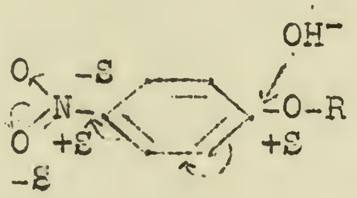


$R-C(OR')_2-OR' + H_2O \rightarrow R-C(=O)-OR' + R'OH$

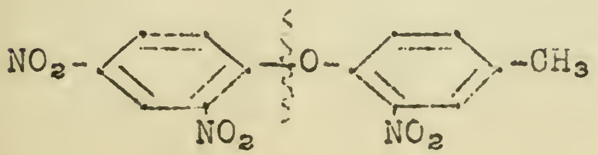
It is well known that the ease of hydrolysis is orthoester > acetal > ether. This may be explained by the increase in stability of the intermediate carbonium ion caused by the increased + E effect of the -OR groups.

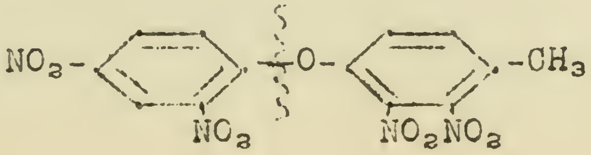
Alkaline Cleavage of Ethers.

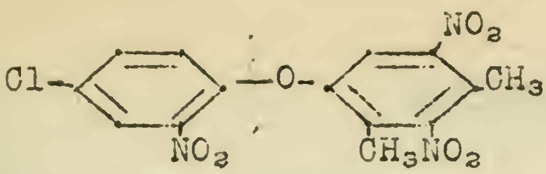
Although the majority of ethers are stable toward alkali, alkaline cleavage is possible in a limited number of cases. In contrast to acidic cleavage, the presence of nitro groups *ortho* or *para* to an ether linkage in an Aralkyl or diaryl ether causes it to be more susceptible to cleavage. This suggests that cleavage occurs by a nucleophilic (S_N2) displacement on carbon since the presence of an electron sink such as the nitro group would create partial positive charges in a position *ortho* or *para* to it, thus promoting attack at these points. It is interesting to note in this respect that *ortho* and *para* nitro anisoles and phenetoles are appreciably cleaved by treatment with 10% KOH while the *meta* isomers remain unchanged.

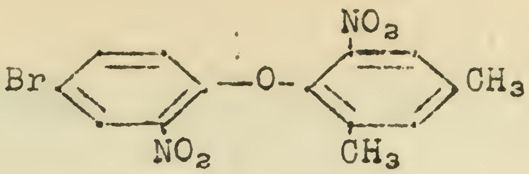


Piperidine has been used in establishing the structure of nitrodiphenyl ethers. Cleavage occurs slowly at 100° when one nitro group is present in the 2 or 4 position, but can be carried to completion in a few minutes with 2,4-dinitrodiphenyl ethers. In practically all cases the amine nitrogen becomes attached to the ring which shows the least density of electrons at the carbon attached to oxygen. That this is not solely a $-I_S$ effect can be seen from the fact that nitro groups in an *ortho* or *para* position are much more effective than those in a *meta* position.

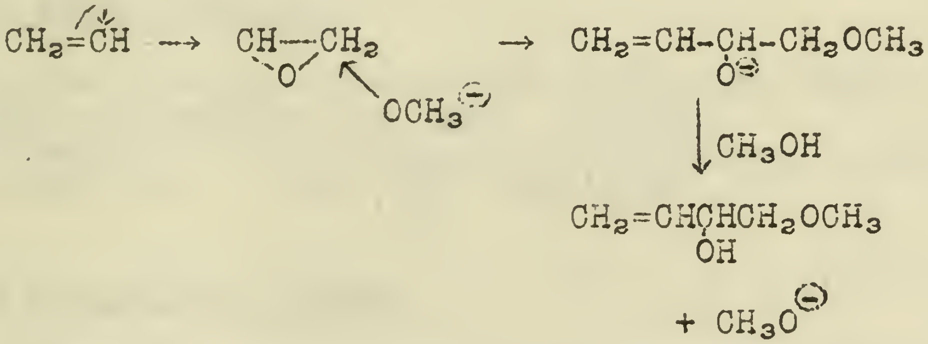








Epoxides may also be cleaved by alkali. This may be illustrated by the cleavage of 3,4-epoxy-1-butene in the presence of a little sodium ethoxide. It was pointed out under acid cleavage that this epoxide cleaves "abnormally" in the presence of acid to give $CH_2{=}CH{-}\underset{OCH_3}{CH}{-}CH_2OH$. However, in the presence of base this compound undergoes the normal cleavage to break the carbon-oxygen bond which has the lowest electron density.



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Base Catalyzed Cleavage of Ethers

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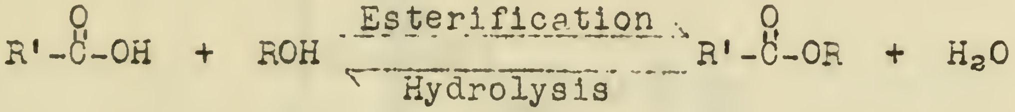
As is well known, esterification, hydrolysis, and ester interchange reactions are equilibrium processes in which the desired products are obtained by displacing the equilibrium



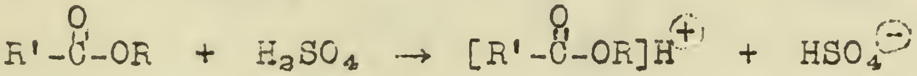
$$R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH + ROH \underset{\text{Hydrolysis}}{\overset{\text{Esterification}}{\rightleftharpoons}} R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR + H_2O$$

by one of several methods. Undoubtedly the same intermediates are involved regardless of the direction in which the reaction proceeds, but since it is experimentally much easier to study hydrolysis than esterification, much more is known about this process. Accordingly this discussion will deal mostly with hydrolysis.

In general the hydrolysis of esters may be carried out with acidic or basic catalysts.

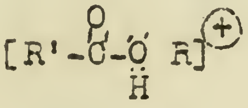
A. Acid Hydrolysis.

It should be remembered that esters are weak bases. When they are dissolved in 100% sulfuric acid, they show a molar depression in freezing point of two as a result of the reaction



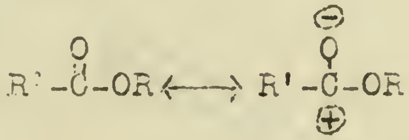
$$R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR + H_2SO_4 \rightarrow [R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR]H^{\oplus} + HSO_4^{\ominus}$$

There has been some question as to the location of the proton in the cation. Most authors in discussing esterification and hydrolysis prefer to put it on the ethereal oxygen and to consider this form as being a necessary and sufficient intermediate in the reaction.



$$[R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}\underset{H}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}}\ R]^{\oplus}$$

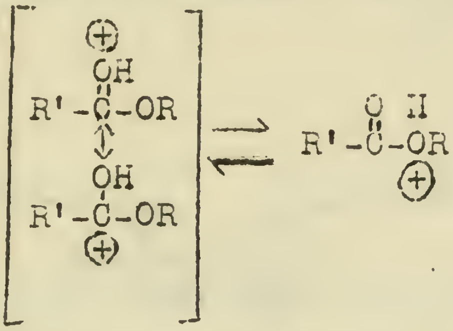
Yet, it is argued, a carbonyl group is known to undergo a mesomeric shift and it would be expected that the addition of a proton would occur largely on the keto oxygen.



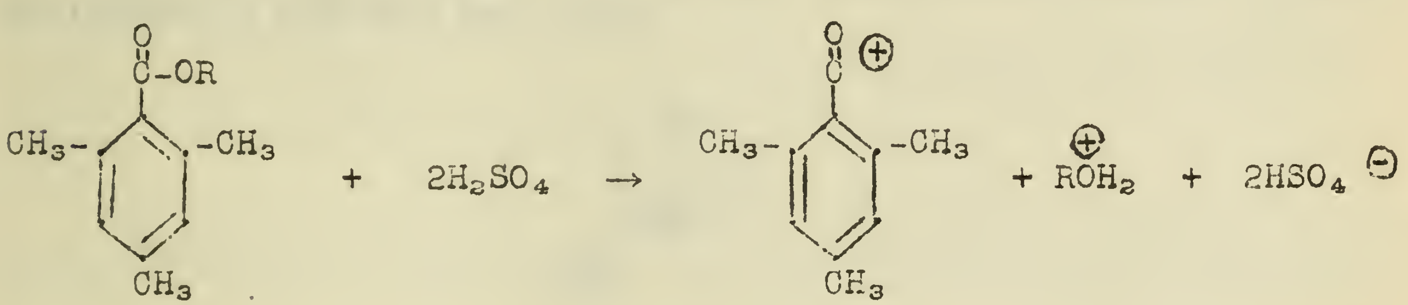
$$R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR \longleftrightarrow R'\text{-}\underset{\oplus}{\overset{\overset{\ominus}{O}}{\overset{|}{C}}}\text{-}OR$$

These two views actually are not incompatible. Although much of the

addition does occur on the keto oxygen, nevertheless it seems reasonable that an equilibrium must exist between the forms


R'-C-OR
OH
R'-C-OR
OH
O H
R'-C-OR

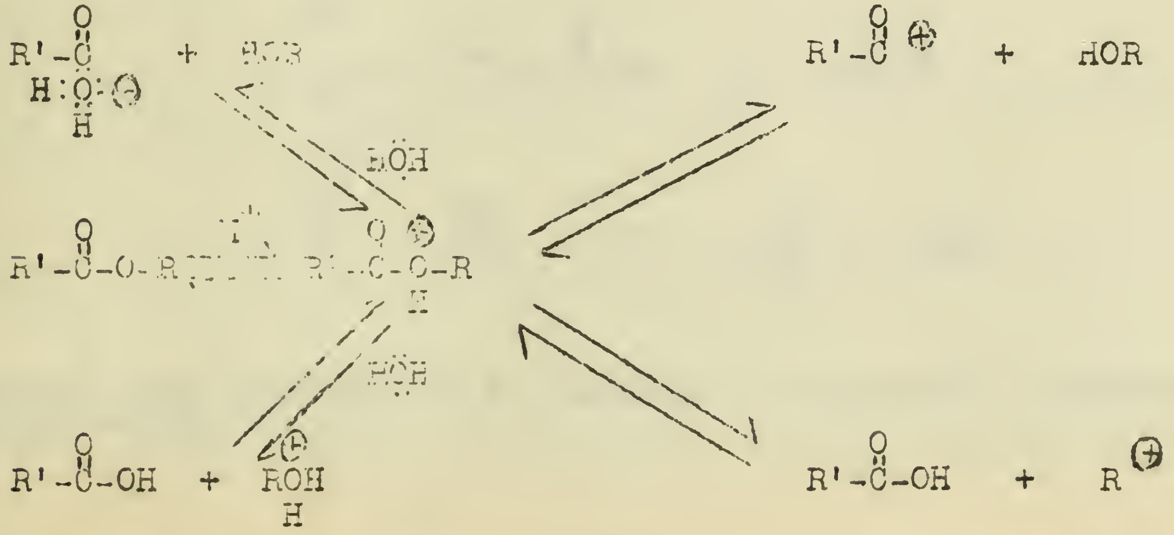
and it is assumed that only when the proton is on the ethereal oxygen, as is shown on the right, does reaction occur. That addition does occur on the ethereal oxygen in certain cases has been unequivocally shown with ethers of 2,4,6-trimethylbenzoic acid. These compounds show a fourfold freezing point depression in sulfuric acid. This can only mean that the reaction shown below has occurred:


C-OR
CH3
CH3
CH3
+ 2H2SO4
CH3
CH3
CH3
+ ROH2
+ 2HSO4

After proton addition has taken place there are four separate and distinct paths by which decomposition of the intermediate may occur. Three of them have been realized:

I. Bimolecular Acyl-Oxygen Fission

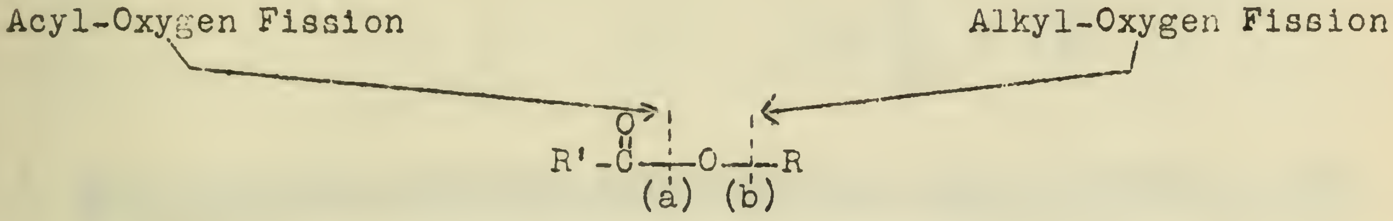
II. Unimolecular Acyl-Oxygen Fission


R'-C
H:O:
H
+ HOR
HOH
R'-C-O-R
H
R'-C-O-R
H
HOH
R'-C-OH
+ ROH
H
R'-C
+ HOR
R'-C-OH
+ R

IV. Bimolecular Alkyl-Oxygen Fission
(Never observed)

III. Unimolecular Alkyl-Oxygen Fission

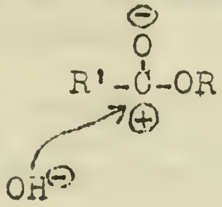
The distinguishing characteristics are whether the reaction is unimolecular or bimolecular after the intermediate has been formed, and whether fission of the acyl-oxygen bond (a) or the alkyl-oxygen bond (b) is involved:



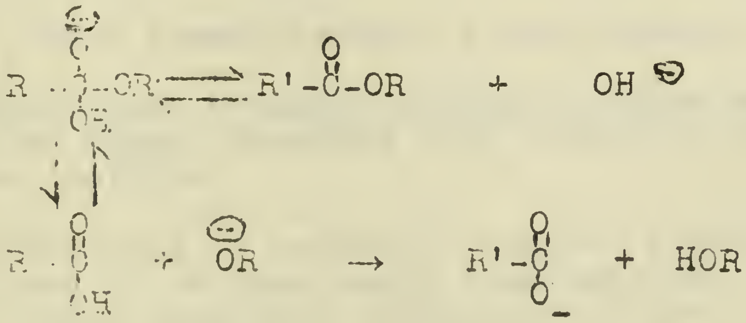
It would not be expected that the effect of substituents on hydrolysis could be predicted without a knowledge of the mechanism involved.

B. Basic Hydrolysis.

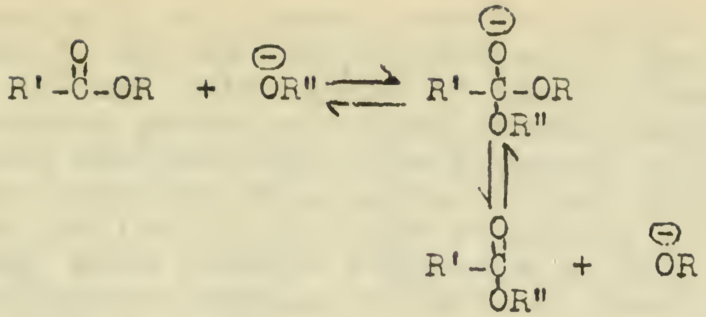
In basic hydrolysis there is only one positive center to which nucleophilic addition can occur:



Decomposition of the addition complex could occur either by the loss of hydroxyl ion (i.e., by a reversal of the step by which it was formed) or by separation of the alkoxide ion. As is well known, the latter reaction proceeds to completion because the equilibrium is displaced by the conversion of the acid into its salt.



When the base employed is an alkoxide ion, however, transesterification occurs:

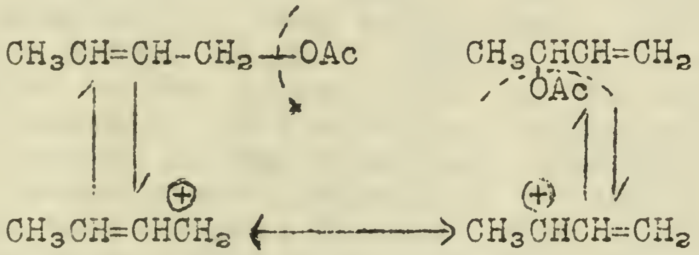


I. Acid Catalyzed Reactions Involving Acyl-Oxygen Fission --- Bimolecular.

Almost all cases of hydrolysis and esterification involving primary and secondary alcohols occur with retention of the bond between the alkyl group R and the ethereal oxygen. Evidence for the prevalence of acyl-oxygen fission is as follows:

(1) In the hydrolysis of optically active O-acetyl malic acid, the asymmetry is retained in the malic acid. If the alkyl-oxygen bond had been broken, the resulting planar carbonium ion would have been expected to undergo at least partial racemization, the amount of racemization increasing with increase in the stability of the carbonium ion under the experimental conditions.

(2) When crotyl- and α-methallyl acetates are hydrolyzed, the carbonium ions, if formed, would represent mesomeric forms. A mixture of products would thus be expected, after addition of water:



Experimentally, this isomerization is not observed.

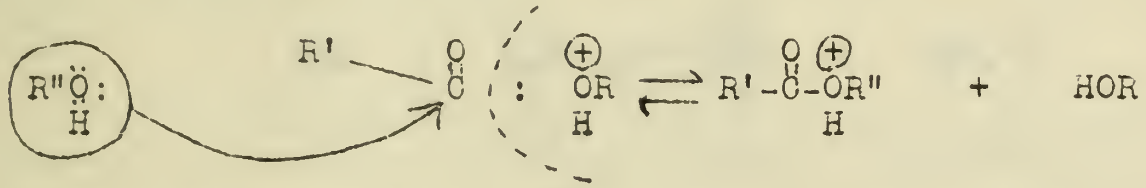
(3) The hydrolysis of amyl acetate in water enriched in the heavy isotopes of oxygen proceeds with formation of the alcohol devoid of these isotopes.

(4) The hydrolysis of neopentyl acetate yields neopentyl alcohol. No amylene or tertiary-amyl compounds are isolated, as would be anticipated had a neopentyl carbonium ion been formed.

This acid-catalyzed reaction is probably third order, the rate of the hydrolysis having been shown, for example, to be proportional to $[H^+]$ [Ester] $[H_2O]$. In general, water will be present in large excess in hydrolysis, as is alcohol in esterification, and the con-

centration of proton will not change, so the reaction will be "pseudo-unimolecular." In the interpretation of the kinetics of esterification and alcohol interchange it must be taken into account that if small amounts of proton are used, small amounts of water entering the reaction will decrease the apparent activity of hydrogen ion, so that the reaction will become slower than expected. Of further interest is the fact that these reactions are catalyzed by all Lewis type acids, such diverse compounds as HCl, "molecular acetic acid" (by difference between total and dissociated acid) and BF_3 exerting a catalytic effect.

The mechanism which best coordinates all these facts is the following, where R, R', and R" may be H or alkyl groups, depending on which of the three reactions is being discussed:



The rate of such a reaction is seen to depend on [R"OH] [H^+ - R'COOR complex], which enter into the slowest, or rate determining step. The concentration of this complex is seen to be linked to the [H^+] [R'COOR] by the equilibrium constant of the reaction involving proton attack, resulting in third order kinetics.

It is difficult to state a priori the effects of substituents on the velocity of such a reaction, since electron release will favor the formation of the protonated complex, but will hinder the nucleophilic attack of R"OH on it. Any substituent, however, would be expected to have more effect if on R' than if on R, since the former is directly attached to the carbon which is the seat of reaction. It is found experimentally that electron releasing groups on R and R' decrease the velocity of the reaction. Possibly this effect is steric, as the rate decreases markedly as R' and R" become more branched. This is true despite the fact that alkyl branching in the alpha position on R" would be expected to increase somewhat the nucleophilic acitivity of R"OH.

II. Acid Catalyzed Reactions Involving Acyl-Oxygen Fission --- Unimolecular.

Certain isolated cases have been found which may be included under this heading:

Although it is extremely difficult to hydrolyze esters of β-isodurylic acid (2,4,6-trimethylbenzoic acid) by more conventional procedures, it was found that dissolving such esters in 100% sulfuric acid and pouring the resulting solutions into water immediately precipitated the corresponding acid. Under identical conditions, esters of benzoic acid dissolve, but precipitate largely unchanged on dilution. Analogously, dissolving the free β-isodurylic acid in [illegible] suggesting a catalytic effect.

The [illegible] in which of the [illegible]

The rate at which a [illegible]

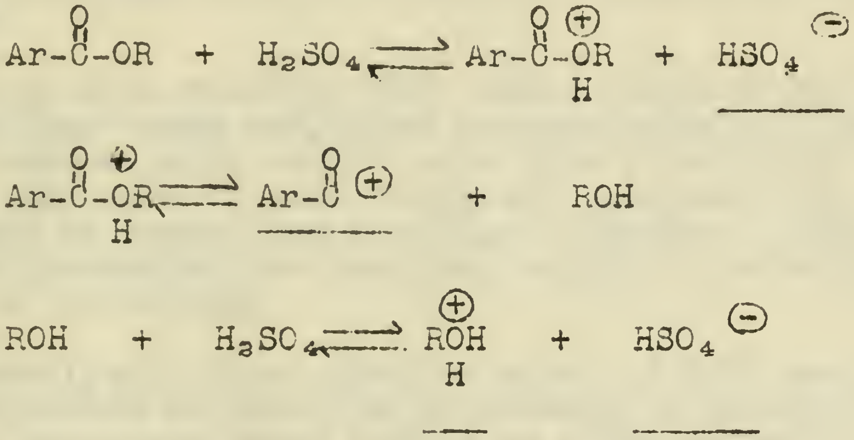
It is difficult to [illegible] a priori the [illegible]

II. Acid [illegible]

[illegible]

[illegible]

100% sulfuric acid and pouring into methanol gives the methyl ester immediately, although more usual esterification procedures again proceed with difficulty. A Van't Hoff (freezing point) depression of nearly four was found for the isodurylic acid in 100% sulfuric acid. As was shown somewhat earlier, this indicates the reaction:

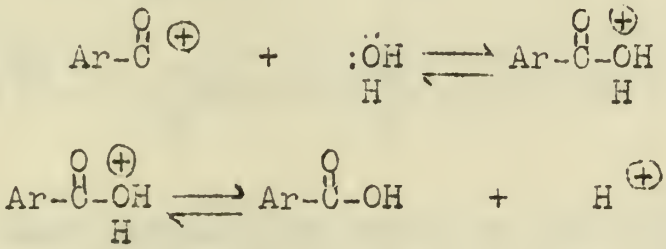


$$Ar-\overset{O}{\overset{\|}{C}}-OR + H_2SO_4 \rightleftharpoons Ar-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{\oplus}{OR}} + \underline{HSO_4^{\ominus}}$$

$$Ar-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{\oplus}{OR}} \rightleftharpoons \underline{Ar-\overset{O}{\overset{\|}{C}}^{\oplus}} + ROH$$

$$ROH + H_2SO_4 \rightleftharpoons \underline{\underset{H}{\overset{\oplus}{ROH}}} + \underline{HSO_4^{\ominus}}$$

The particles responsible for the freezing point depression have been underlined. Then with addition to water:



$$Ar-\overset{O}{\overset{\|}{C}}^{\oplus} + \underset{H}{:\ddot{O}H} \rightleftharpoons Ar-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{\oplus}{OH}}$$

$$Ar-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{\oplus}{OH}} \rightleftharpoons Ar-\overset{O}{\overset{\|}{C}}-OH + H^{\oplus}$$

This mechanism would be expected to be detectable only in highly polar, extremely acid solvents, on esters of acids capable of a large electron release to stabilize the acyl carbonium ion. Indeed, it was found that the corresponding dimethyl benzoic acids gave Van't Hoff factors indicating less than four particles per molecule of substituted benzoic acid. Thus the I_D effect of three methyl groups is required for this reaction to occur. The reaction would not be expected to be subject to steric hindrance, as (1) the first addition is to the oxygen, which itself is not considerably hindered by ortho (methyl) groups; and (2) subsequent reaction is by a unimolecular mechanism, requiring no attack by any other reagent.

III. Acid Catalyzed Reactions Involving Alkyl-Oxygen Fission --- Unimolecular.

It is to be expected that such a reaction would proceed with partial racemization of an alcohol asymmetric at the point of at-

[illegible] acid and reaction [illegible] gives the [illegible] immediately, although more rapid [illegible] proceeded again [illegible] with difficulty. A [illegible] giving [illegible] of nearly [illegible] for the [illegible] acid. As the [illegible]:

[illegible]

[illegible]

[illegible]

The reactions, presumably for the [illegible] parts. [illegible] have been established. These will [illegible] as follows:

[illegible]

[illegible]

This explanation [illegible]

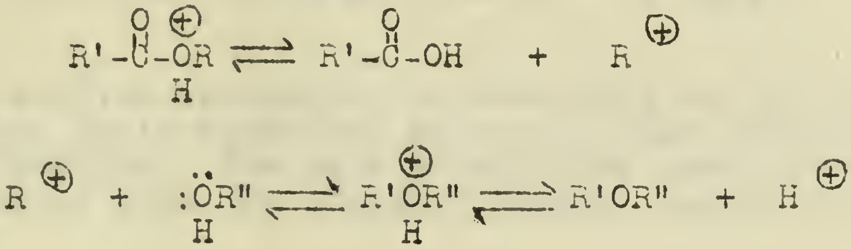
III. [illegible]

It is to be expected that [illegible]

tachment of the oxygen. Further, the reaction would be likely to occur in the order: tert. alcohol > secondary > primary, both because of the inherently greater stability of carbonium ions in that order, and because the rate of the alternative bimolecular acid-catalyzed mechanism involving acyl-oxygen fission is in the reverse order. In common with other unimolecular reactions and in contrast to bimolecular reactions, the rate should be largely unaffected by steric hindrance.

Indications of this reaction were first found in the observation that the sulfuric acid catalyzed esterification of active secondary octyl alcohol with acetic acid gave a partially racemized ester. Further, the rate of acid catalyzed hydrolysis of the acetic acid esters of ROH decreases for R = $CH_3- > CH_3CH_2- > (CH_3)_2CH-$, but again starts increasing for tertiary butanol, indicating a probable change of mechanism.

Although hydrolysis of an inactive ester of this mechanism would give no direct chemical evidence of mechanism, it is seen from the following that alcoholysis would result in ether formation:



$$R'-\overset{O}{\overset{\|}{C}}-\overset{\oplus}{\underset{H}{O}}R \rightleftharpoons R'-\overset{O}{\overset{\|}{C}}-OH \quad + \quad R^{\oplus}$$

$$R^{\oplus} \quad + \quad :\underset{H}{\ddot{O}}R'' \rightleftharpoons R'\overset{\oplus}{\underset{H}{O}}R'' \rightleftharpoons R'OR'' \quad + \quad H^{\oplus}$$

An ideal test for this possibility would be the alcoholysis of a tertiary-butyl ester of β-isodurylic acid, since the bimolecular acyl-oxygen fission mechanism is inhibited by steric factors, and the unimolecular reaction with acyl-oxygen fission, at least in the case of the methyl esters of this acid, does not operate is sulfuric acid appreciably below 100% in strength. It has been found that tertiary-butyl trimethylbenzoate is rapidly hydrolyzed by 40% methanolic HCl at room temperature, giving a nearly quantitative yiel of acid, and also methyl tertiary-butyl ether. Under similar conditions, a mixture of methanol and t-butyl alcohol did not give appreciable amounts of the ether. The isopropyl ester also could be hydrolyzed by refluxing with the same concentration of methanolic HCl, but the methyl ester was found to be totally inert under these conditions. It was also found that the t-butyl ester could be slowly hydrolyzed by refluxing with methanol alone, again giving appreciable amounts of the ether. Further evidence of carbonium ion intermediates was the formation of butene and rearranged butanol derivatives in some cases.

These facts are taken as evidence for the unimolecular mechanism involving alkyl-oxygen fission, catalyzed by protons initially supplied by the methanol, and later by acid formed during the reaction.

increment of the oxygen. However, the reaction would be likely to occur in the order: tert. alcohol > secondary > primary, because of the inherently greater stability of carbonium ions in this order, and because the rate of the kinetically bimolecular acid-catalyzed mechanism involving acyl-oxygen fission is in the reverse order. In common with other unimolecular reactions, and in contrast to bimolecular reactions, the rate should be largely unaffected by steric hindrance.

Indications of this reaction were first found in the investigation that the sulfuric acid catalyzed esterification of active secondary octyl alcohol with acetic acid gave a partially racemized ester. Further, the rate of this esterification [illegible] of the acetic acid, [illegible] of RCOOH decreases for R = [illegible], but again slowly increasing for tertiary-butyl, indicating a probable change of mechanism.

Although hydrolysis of an optically active ester of this mechanism would give no direct chemical evidence of mechanism, it is seen from the following that alcoholysis would result in ether formation:

$$R'C\overset{\oplus}{\underset{R}{O}}H \rightleftharpoons R'COOH + R^{\oplus}$$

$$R^{\oplus} + :\underset{H}{O}R'' \rightleftharpoons R\overset{\oplus}{\underset{H}{O}}R'' \rightleftharpoons ROR'' + H^{\oplus}$$

An ideal test for this possibility would be the alcoholysis of a tertiary-butyl ester of 2,4,6-trimethylbenzoic acid. The [illegible] acyl-oxygen fission mechanism is inhibited by steric factors, as the unimolecular reaction [illegible] of this acid, [illegible] with hydrolysis being 100% in [illegible]. It was found that tertiary-butyl 2,4,6-trimethylbenzoate is readily [illegible] in 1% methanolic HCl at room temperature, giving [illegible] of acid, and also methyl tertiary-butyl ether. [illegible] a mixture of methanol and [illegible] quantitative [illegible] of the ether. The [illegible] hydrolyzed by refluxing with the same [illegible] of methanolic HCl, only the [illegible] was found to be [illegible] conditions. It was also found that the [illegible] hydrolyzed by refluxing with methanol [illegible] of the ester. Further [illegible] indicate that the formation of ethers and [illegible] reactions in some cases.

These facts are taken as evidence for the [illegible] unimolecular alkyl-oxygen fission, [illegible] by [illegible] and later by [illegible] during the esterification.

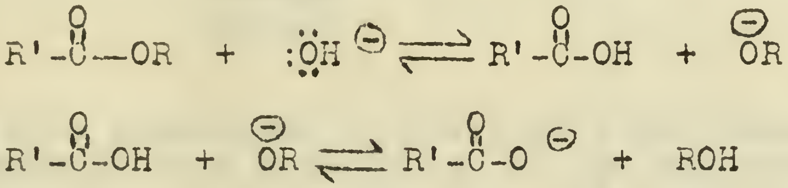
IV. Acid Catalyzed Reactions Involving Alkyl-Oxygen Fission --- Bimolecular.

This mechanism has never been observed.

V. Base Catalyzed Reactions Involving Acyl-Oxygen Fission --- Bimolecular.

Evidence similar to that outlined for the acid catalyzed reactions indicates that saponification of esters occurs ordinarily with acyl-oxygen fission.

Saponification is kinetically of second order, proportional to [Ester] [OH⁻], and so probably has the mechanism:



$$R'-\overset{\overset{O}{\|}}{C}-OR + :\ddot{\underset{\cdot\cdot}{O}}H^{\ominus} \rightleftharpoons R'-\overset{\overset{O}{\|}}{C}-OH + \overset{\ominus}{O}R$$

$$R'-\overset{\overset{O}{\|}}{C}-OH + \overset{\ominus}{O}R \rightleftharpoons R'-\overset{\overset{O}{\|}}{C}-O^{\ominus} + ROH$$

Since the second reaction is largely irreversible and so drives the first to completion, it is clear why base catalyzed esterification is not generally feasible. The rate determining step is aided by recession of electrons from the carbonyl carbon, and is subject to steric hindrance.

Increasing electron withdrawal by R or R' should promote the reaction since the attacking reagent in the first step is nucleophilic. This was borne out by a study of rates of saponification of *para*-substituted benzoic esters in which the rates were found to vary with the *para* substitutent as follows:

$$NO_2 > Cl > H > CH_3 > NH_2$$

$$\longleftarrow$$

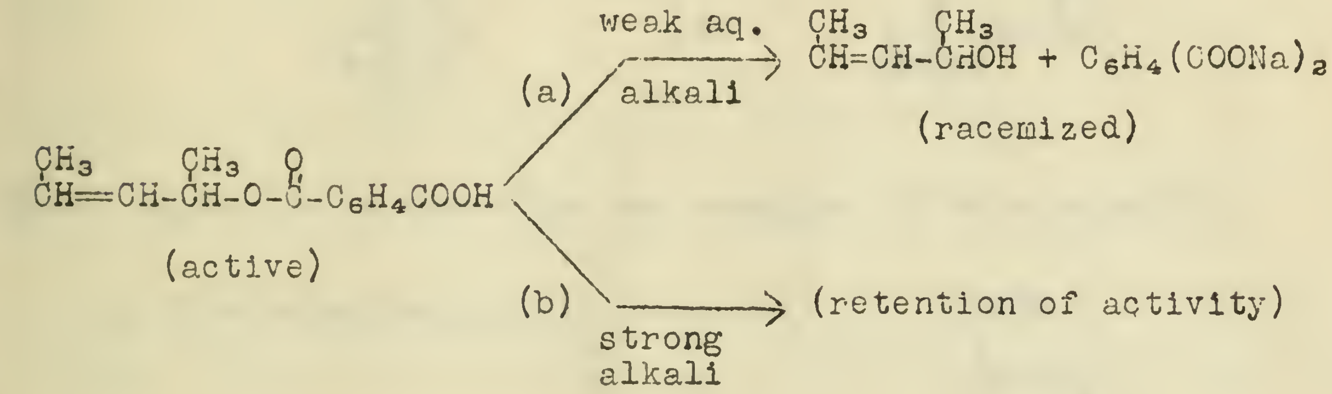
Increasing electron withdrawal
Increasing reaction rate

VI. Base Catalyzed Reactions Involving Acyl-Oxygen Fission --- Unimolecular.

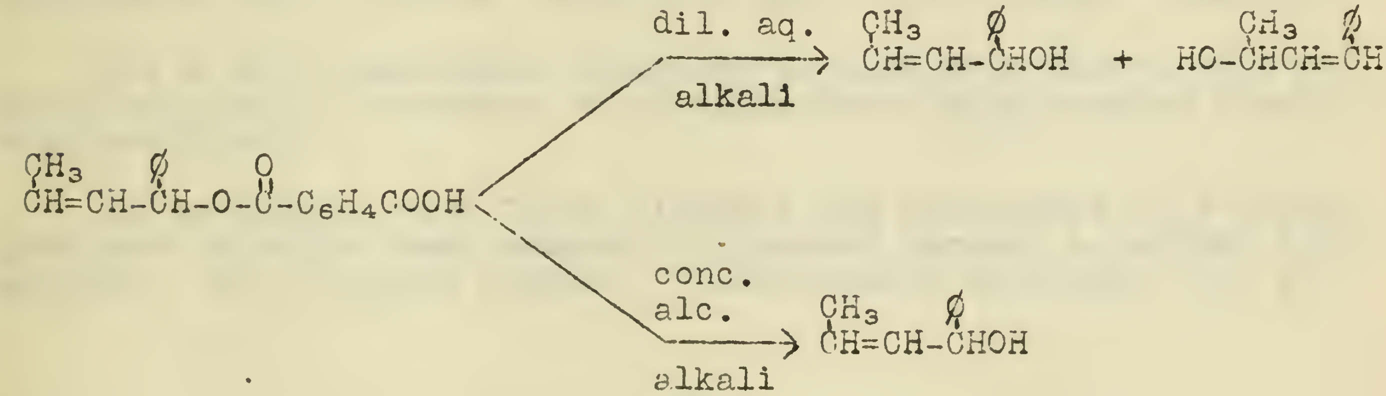
No examples of this mechanism have as yet been established.

- - - - - - -

It should be noted that the mechanism of hydrolysis or esterification is not necessarily determined completely by the acidity of the medium. The hydrolysis of certain substituted allyl alcohols has been shown to yield:


CH3 CH3 O
CH=CH-CH-O-C-C6H4COOH
(active)
(a)
weak aq.
alkali
CH3 CH3
CH=CH-CHOH + C6H4(COONa)2
(racemized)
(b)
strong
alkali
(retention of activity)

Reaction (a) has been postulated to occur by a new unimolecular mechanism, but probably is a combination of the alkaline bimolecular reaction (retention of activity) with the acid catalyzed unimolecular mechanism. The acid catalyzed unimolecular mechanism would be aided by the stabilization of allylic carbonium ions by the resonance previously discussed, and so might proceed even in slightly basic solutions. Predominant inversion ("shielding effect"), racemization, and rearrangement would result from this acid mechanism.

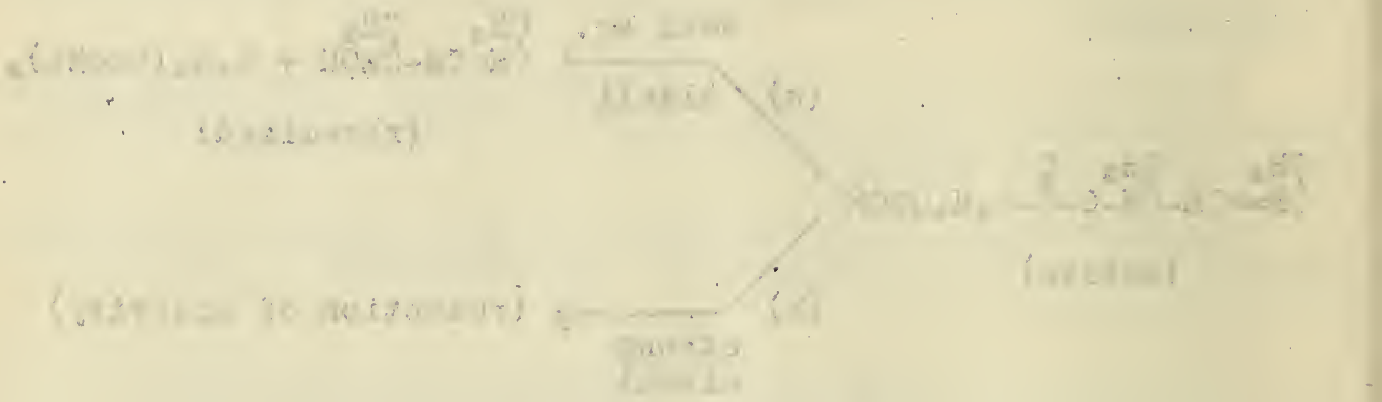

CH3 Ø O
CH=CH-CH-O-C-C6H4COOH
dil. aq.
alkali
CH3 Ø
CH=CH-CHOH
+
CH3 Ø
HC-CHCH=CH
conc.
alc.
alkali
CH3 Ø
CH=CH-CHOH

VII. Hydrolysis of Lactones.

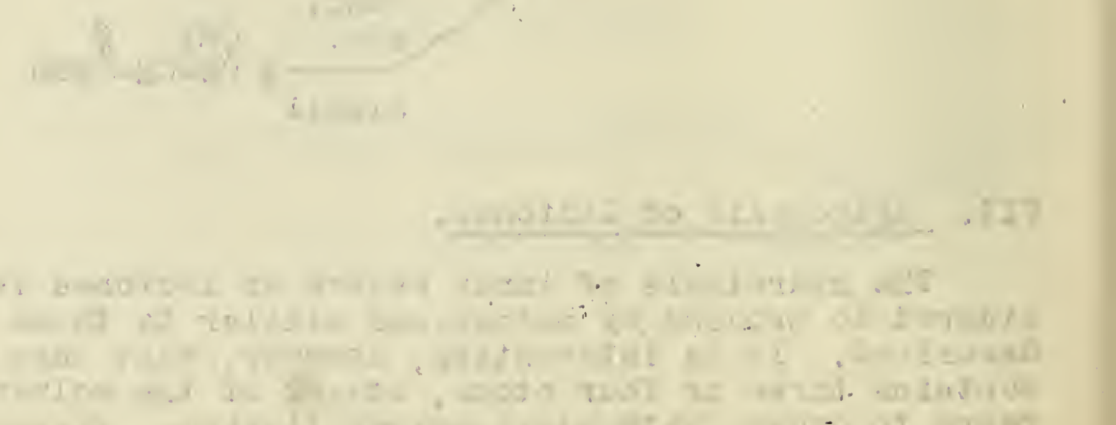
The hydrolysis of inner esters or lactones is usually considered to proceed by mechanisms similar to those which have been described. It is interesting, however, that when the lactone ring contains three or four atoms, attack of the solvent molecule appears to occur, with alkyl-oxygen fission. Presumably this is due to strain in the three or four membered ring.

(III)

It should be noted that the mechanism of hydrolysis or esterification is not necessarily determined absolutely by the acidity of the medium. The hydrolysis of certain substituted [illegible] ketones has been shown to yield:

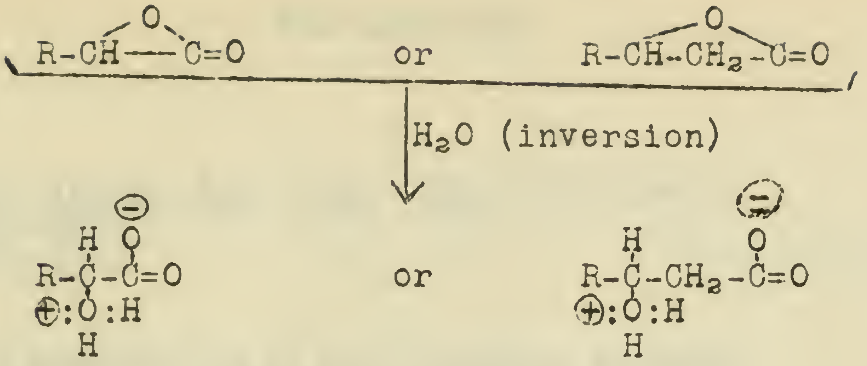


Reaction (a) and (b) [illegible] mechanism, but probably is a combination of the [illegible] reaction (referring to [illegible]) with the acid [illegible] mechanism. The acid-catalysed [illegible] would be expected as the [illegible] of [illegible], the apparently [illegible], [illegible] slightly [illegible] reactions. [illegible] [illegible], and [illegible] from this acid [illegible].



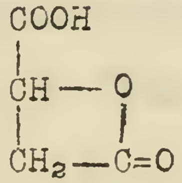
VII. Hydrolysis of Ketones.

The hydrolysis of these ketones is [illegible] readily [illegible] and similar to those which have been described. It is interesting, however, that [illegible] three or four steps, [illegible] to [illegible] it is not [illegible] in the [illegible].

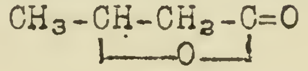


There appear to be two clear cut examples of this behavior:

1. β-malolactonic acid



2. β-Butyrolactone



$CH_3-CH-CH_2-C=O$

Both of these compounds show

(a) A rapid, alkaline hydrolysis which occurs with retention of configuration (base catalyzed - acyl-oxygen fission).

(b) A rapid acid catalyzed hydrolysis which occurs with retention of configuration (acid catalyzed - acyl-oxygen fission).

(c) A slow hydrolysis occurring in extremely dilute acid and characterized by inversion of configuration (Alkyl-oxygen fission - acid catalyzed).

In accordance with these findings the hydrolysis of α-bromopropionic acid has been assumed to proceed through a lactone intermediate. (cf. Organic Seminar, "Displacement Reactions," p. 8),

Bibliography

General.

Day and Ingold, Trans. Far. Soc., 37, 687 (1941).
Remick, pp. 394-408.
Watson, pp. 125-131.

Acid Catalyzed Reaction with Alkyl-Oxygen Fission.

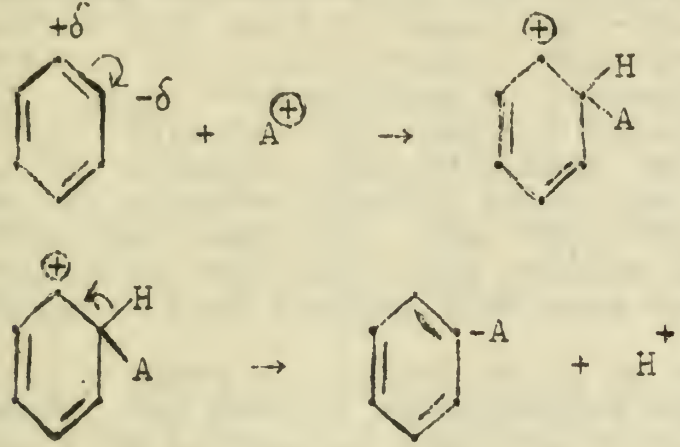
Organic Seminars, 20, 10.

Influence of Course of Reaction on Steric Configuration of Products.

Cowdrey, Hughes, Ingold, Masterman, and Scott, J. Chem. Soc., 1252 (1937).

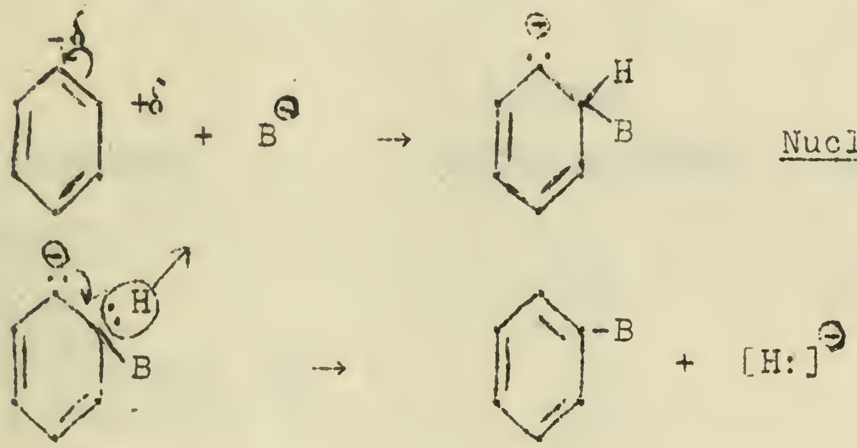
An ionic attack, resulting in the elimination of hydrogen from an aromatic nucleus, might be expected to take place by either of the following mechanisms:

(1)



Electrophilic Substitutio

(2)



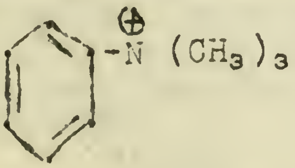
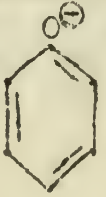
Nucleophilic Substitution

(a hydride ion)

Both of these reaction mechanisms are known. Inspection of mechanism (1) gives rise to these considerations:

(A) A positively charged substituent on the ring must increase the free energy of the transition state, thereby decreasing the rate of reaction.

(B) Conversely, a negatively charged substituent must result in the increased activity of the ring.

Since the majority of substitution reagents react very slowly with  and very rapidly with  we may suppose that most substitutions are initially electrophilic attacks.

Electrophilic Substitution

Activation and Deactivation. From our earlier discussions of the electrical effects which can operate within a molecule we see that four effects must be taken into consideration in the process of activation and deactivation. They have been designated I_s, I_D, E, and M. It is evident from an inspection of (1) that any substituent which increases the electron density at one of the carbon atoms of the aromatic ring will cause activation while groups which decrease the electron density about one of the carbon atoms will deactivate that position. When the effects operate in such a way as to reinforce each other the problem of predicting activation and orientation is much simpler than when they operate in opposition.

Table I shows the effect of I_s on ring activation. In accord with theory, the rate of chlorination of p-chlorophenyl ethers decreases with decreasing electron release of the -OR group.

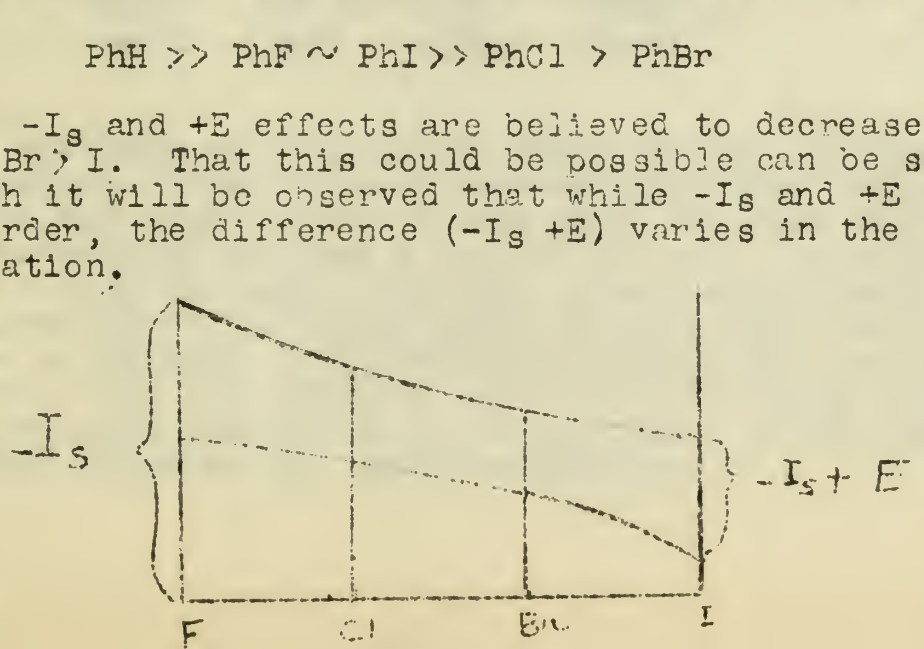
Table I

Compound	Entering Group	Velocity Constant
p ClC_6H_4OPr	Cl	2.76
p ClC_6H_4OEt	Cl	2.44
p ClC_6H_4OMe	Cl	1.23
p $ClC_6H_4OCH_2Ph$	Cl	0.83
p $ClC_6H_4OCH_2C_6H_4Cl$ (p)	Cl	.48
p $ClC_6H_4OCH_2C_6H_4NO_2$ (p)	Cl	.17

When the inductive effects (I_D, I_S) and the electromeric (E) or mesomeric effect (M) operate in opposition it is interesting that the prediction of activation or deactivation is impossible until magnitudes may be assigned each of these quantities. Uusually, however, the E or M effects have been found to outweigh the inductive effects. The nitration of the halobenzenes can serve as an example of this behavior. The rate of nitration is in the order:

$$PhH >> PhF \sim PhI >> PhCl > PhBr$$

Yet the $-I_s$ and +E effects are believed to decrease in the order $F > Cl > Br > I$. That this could be possible can be seen from Figure 1 in which it will be observed that while $-I_s$ and +E decrease in the above order, the difference ($-I_s$ +E) varies in the order of the rates of nitration.



In Table II is summarized the relation of I and E effects to orientation and activation.

Table II

Substituent	Orientation	Activation	Examples
+I only	o, p	+	$-C(CH_3)_3$
-I only	m	-	$-CCl_3$
+I, +E, M	o, p	+	$-O^-$
-I < +E, M	o, p	+	$-OR$, $-NR_2$
-I > +E, M	o, p	-	halogen
-I, -E, M	m	-	$-NO_2$, $-CO_2R$

Factors Influencing the Ratio of Para to Ortho Substitution

Thus far we have made no attempt to discuss the factors influencing the ratio of para to ortho substitution. From a statistical point of view, the ratio p/o should be 0.5 by virtue of the two ortho positions to the one para position. Accordingly, the ratio will be greater or less than 0.5 depending on whether para or ortho substitution is favored. In Table III it can be seen that a considerable difference in the ratio is observed.

Table III

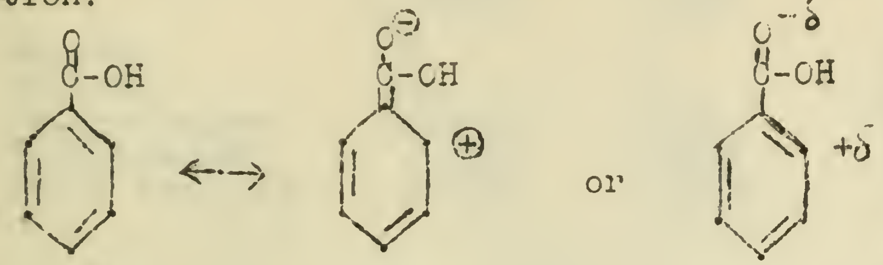
Ratio of Para to Ortho Substitution Accompanying Nitration

Substance	Ortho %	Para %	p/o	Substance	Ortho %	Para %	p/o
PhF	12.4	87.6	7.06	PhMe	58	38	0.65
PhCl	30.1	69.9	2.32	$PhCH_2Cl$	41	55	1.34
PhBr	37.6	62.4	1.66	$PhCHCl_2$			1.84
PhI	41.1	58.7	1.43	$PhCCl_3$			4.22

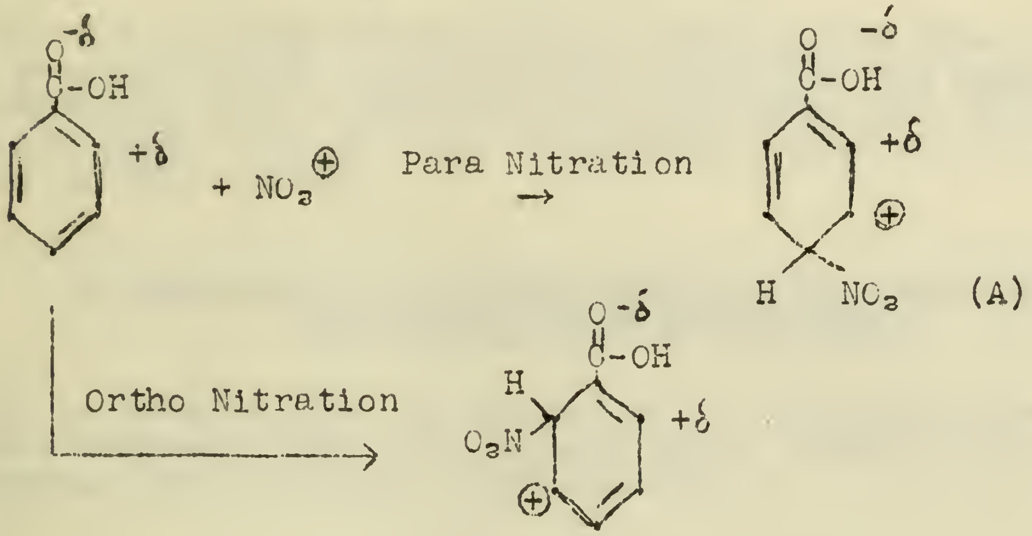
It has been pointed out by Lapworth and Robinson that much of this data can be explained by recognizing that inductive effects will influence the ortho position more than the more distant para position. Thus substituents showing a $+I_s$ effect will activate the ortho position more than the para position. Also substituents showing a $-I_s$ effect deactivate the ortho position more than the para position. The case of toluene is interesting because the fact that the ratio is greater than 0.5 suggests that the activating influence of the methyl group is not due to I_s or I_D only. It has been interpreted as further evidence for hyperconjugation.

The nitrations of benzoic acid and aromatic ketones are examples of a number of cases in which substituents show much smaller p/o ratios than would be expected. One possible explanation is to be found in an examination of the transition state complex which is formed on nitration:

(3)



(4)



(More stable than A)

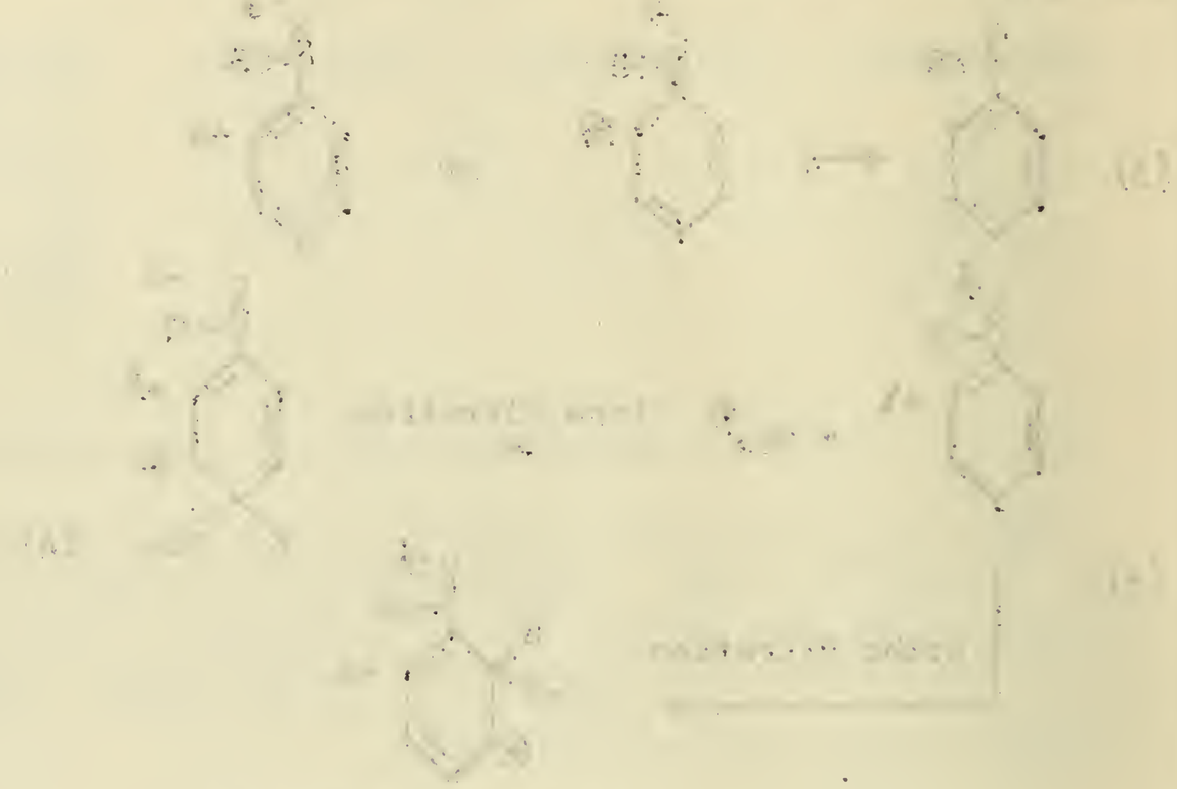
When nitration occurs in the para position adjacent atoms carry positive charges while in the case of ortho nitration a resonance hybrid may be written in which the positive centers occur on more remote carbon atoms. The second of these structures is normally considered to be much more stable (Resonance p. 2) with the result that ortho nitration is favored.

More quantitative data support these general considerations. By determining the rates of nitration of benzene and a substituted benzene derivative in a 1-1 reaction mixture and then measuring the proportion of products obtained when the substituted benzene derivative is nitrated alone, it is possible to get a measure of the rate of substitution at various positions of the substituted derivative in comparison to benzene. This quantity is called the "Partial Rate Factor."

$$\text{Partial Rate Factor (para position)} = \frac{\text{Rate of substitution at position 4 of derivative}}{\text{Rate of substitution of benzene}}$$

In Table IV is shown the partial rate factors for a number of compounds.

[illegible]



[illegible]

[illegible]

[illegible]

Partial Rate Factor = $\frac{\text{Rate of substitution of particular position}}{\text{Rate of substitution of benzene}}$
(para position)

In Table IV is given [illegible] compounds.

Table IV

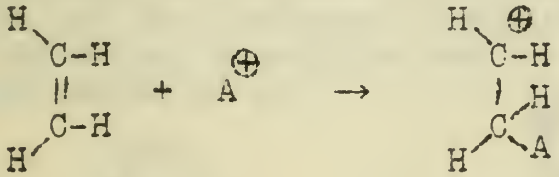
Partial Rate Factors for Nitration by Acetyl Nitrate

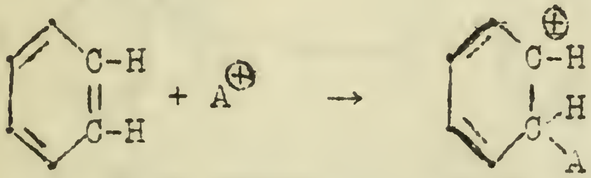
	Ortho	Meta	Para
Benzene	1	1	1
Toluene	43	3	55
Chlorobenzene	0.030	0.000	0.139
Bromobenzene	0.037	0.000	0.106
Ethyl benzoate	0.0026	0.0079	0.0009

It will be observed that these measurements show the methyl group to activate all positions but particular the *ortho* and *para*. The carbethoxy group deactivates all positions but particularly the *ortho* and *para*. All of these measurements support the conclusions we have already reached.

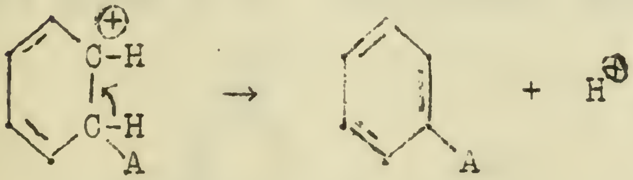
A Comparison of Aromatic Substitution and Addition to Carbon-Carbon Double Bonds

It is obvious that the mechanism for aromatic substitution that has been suggested here involves the usual electrophilic attack on an olefinic bond to form a carbonium ion.

(5)


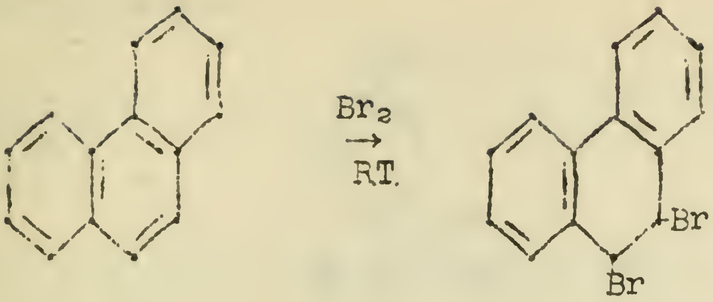
(6)


In the case of the aromatic compound a proton is eliminated so as to restore the Kekule resonance.

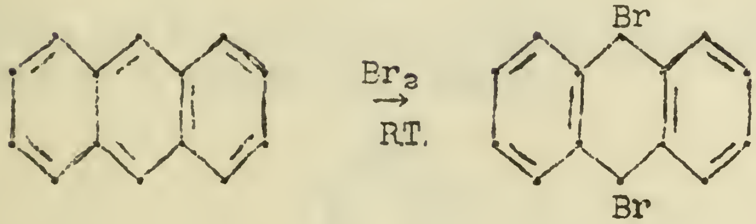
(7)


Since the elimination reaction is favored by the restoration of the aromatic ring, it is a consequence of this mechanism that when the resonance energy lost is particularly low, subsequent addition of an anion (say Br^-) might occur more rapidly than elimination. It is well known that this possibility has been realized in the bromination of phenanthrene and anthracene at positions where the resonance energy lost is small.

(8)

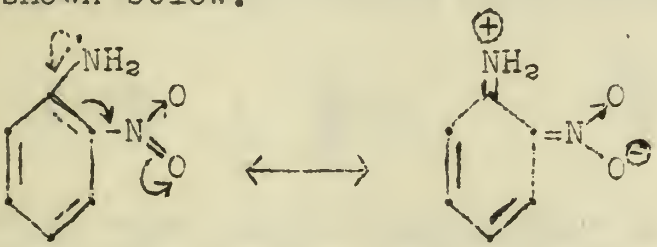


(9)



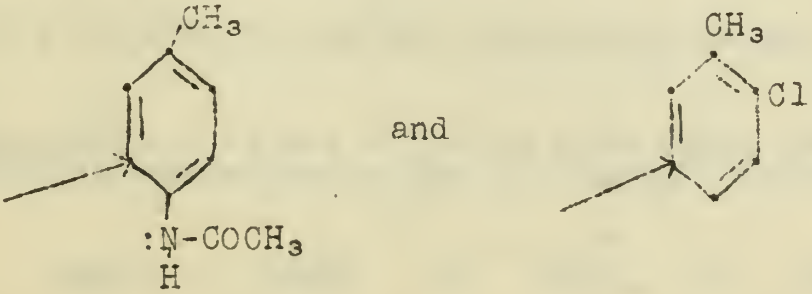
Competitive Reactions.--One of the problems of aromatic substitution which has long been of interest is the position an entering group takes when two groups are acting in opposition to one another. Originally it was believed that the proportion of isomer formed could be predicted from a knowledge of the relative rates of reaction of the monosubstituted benzenes. Qualitatively this is true but it is now recognized that there is frequently an interaction between certain groups which destroys any quantitative relationship. Thus the proportion of isomers produced in the nitration of ortho nitroaniline could not be predicted quantitatively from a comparison of the rate of nitration of aniline and nitrobenzene because of the resonance forms shown below.

(10)



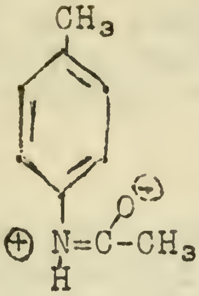
In this connection there appears to be one rule of general application which has been pointed out by Robinson. When a substituent possesses at least one pair of free electrons on an atom next to a benzene ring, it will control the direction of orientation when an alkyl group is in opposition. Thus:

(11)

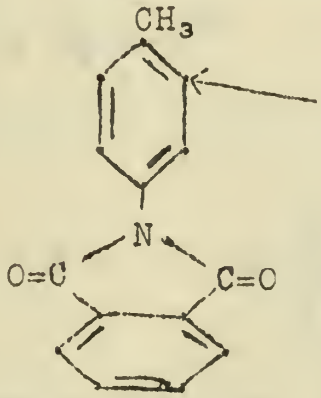


It is interesting that the acetamino group outweighs the methyl group since the electron release toward the ring is lowered by the

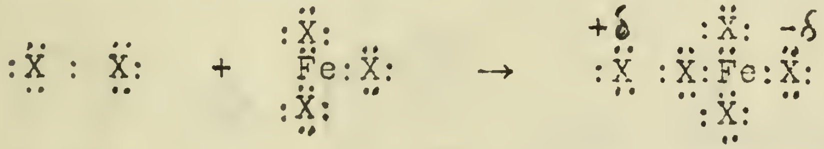
resonance hybrid:



The rule fails when this tendency is further enhanced by the introduction of a second acyl group.

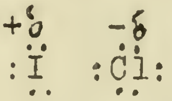


Halogenation.--It is well known that aromatic halogenation is facilitated by certain metal halides (FeX_3, SbX_5, AlX_3, etc.). It is the purpose of these salts to enhance the electrophilic character of the halide by the charge separation:

(12) 

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}: \quad + \quad \begin{array}{c} :\overset{\cdot\cdot}{X}: \\ \overset{\cdot\cdot}{Fe}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}: \\ :\underset{\cdot\cdot}{X}: \end{array} \quad \rightarrow \quad \overset{+\delta}{:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}} \quad \begin{array}{c} :\overset{\cdot\cdot}{X}: \quad -\delta \\ :\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}:\overset{\cdot\cdot}{Fe}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{X}}: \\ :\underset{\cdot\cdot}{X}: \end{array}$$

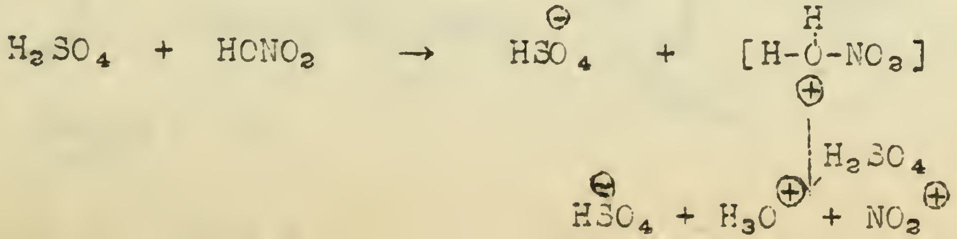
Similarly, when iodine monochloride is the halogenating agent employed, iodine rather than chlorine will be introduced into the aromatic ring as a result of the unequal charge distribution between the dissimilar halogen atoms.



$$\overset{+\delta}{:\underset{\cdot\cdot}{\overset{\cdot\cdot}{I}}} \quad \overset{-\delta}{:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:}$$

It is not understood why IBr brominates phenol and aniline.

Nitration.--It has recently been shown that the active agent in nitration reactions is the ion $[NO_2]^+$ formed by the reaction

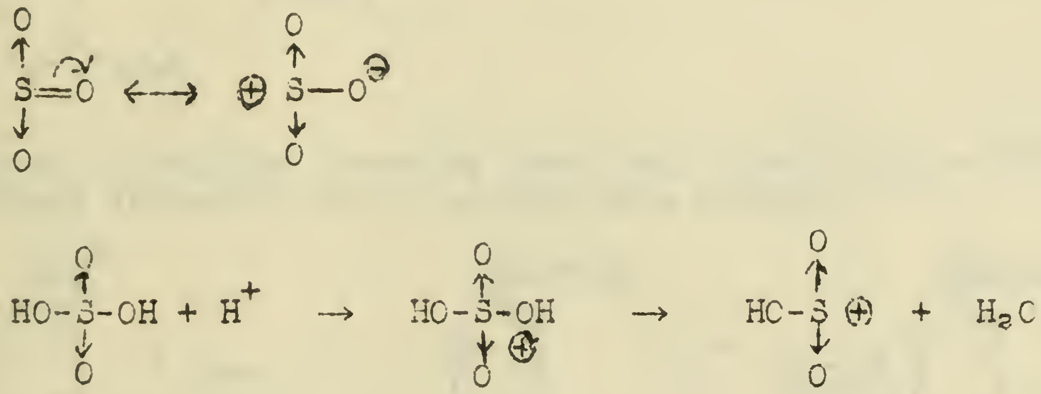
(13) 

$$H_2SO_4 + HONO_2 \rightarrow \overset{\ominus}{HSO_4} + [H-\underset{\oplus}{\overset{H}{O}}-NO_2] \xrightarrow{H_2SO_4} \overset{\ominus}{HSO_4} + H_3O^{\oplus} + NO_2^{\oplus}$$

The purpose of sulfuric acid in the usual nitrating mixture is therefore to provide a strongly acidic medium to promote this ionization. That it does not act as a dehydrating agent as is commonly believed can be illustrated by the fact that when phosphoric anhydride is introduced into the reaction mixture there is no change in the reaction rate.

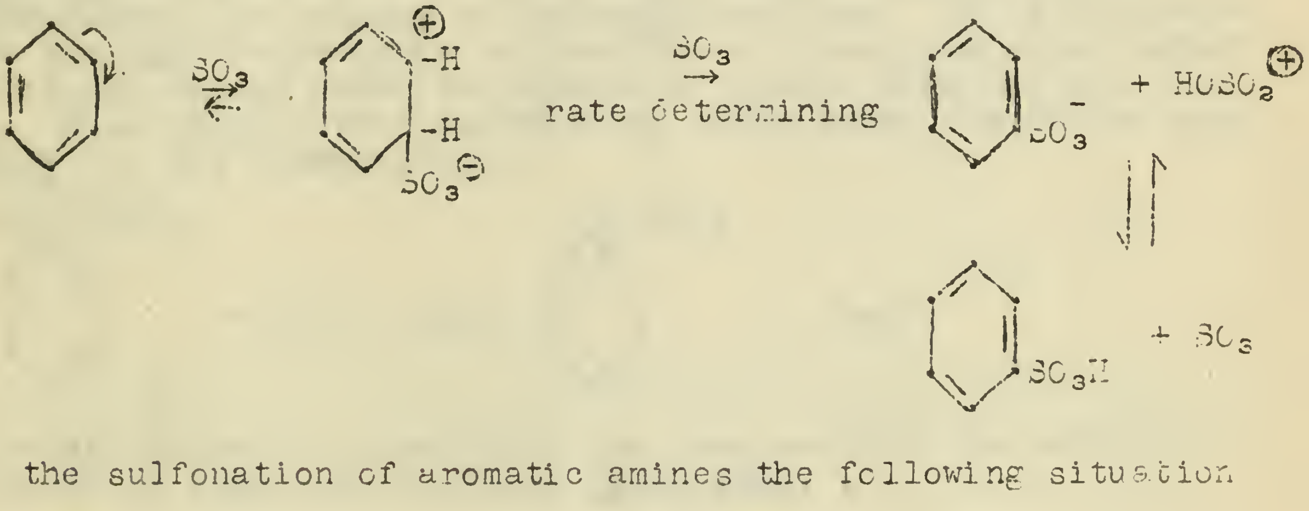
Sulfonation.--In sulfonation reactions there appear to be two species capable of initiating the reaction - sulfuric acid and sulfur trioxide. Both of these reagents are electrophilic in character.

(14)


HO-S-OH + H+
HO-S-OH
HC-S ⊕ + H₂C

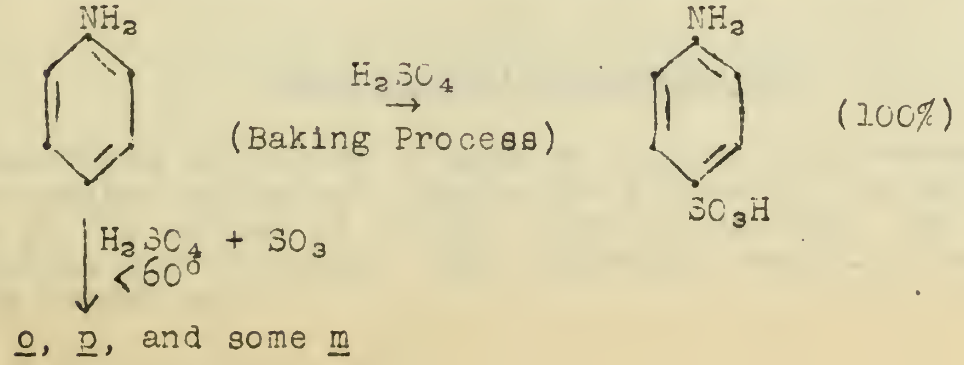
In nitrobenzene solution, sulfonation experiments with sulfur trioxide show that the rate is proportional to the square of the sulfur trioxide concentration. This has been interpreted as involving the complex S_3O_6. Perhaps a more reasonable way of viewing the reaction is to suppose that the elimination of the proton is the rate-determining step which requires the acceptor SO_3.

(15)

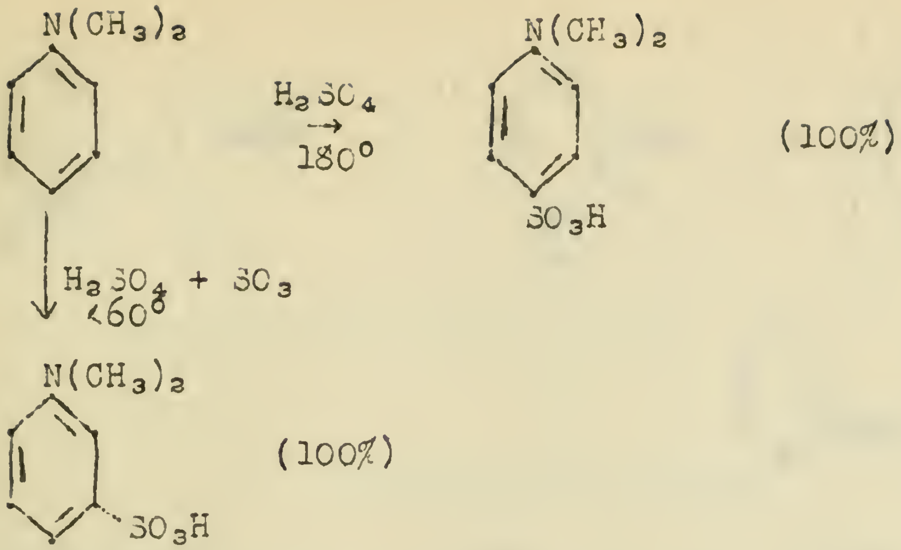

SO₃
-H
-H
SO₃
SO₃
rate determining
SO₃
+ HOSO₂
SO₃H
+ SO₃

In the sulfonation of aromatic amines the following situation exists:

(16)

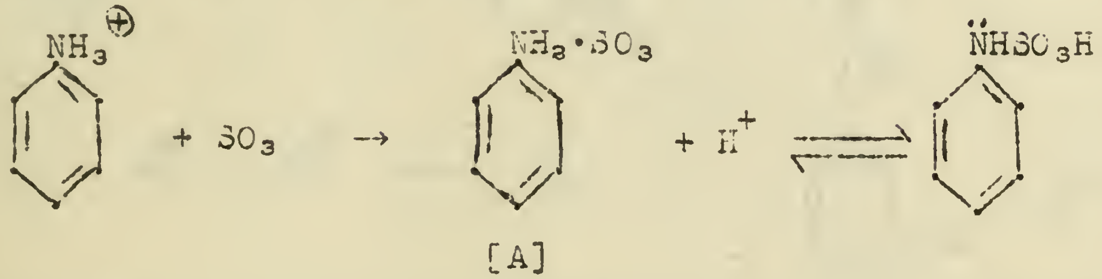

NH₂
H₂SO₄
(Baking Process)
NH₂
SO₃H
(100%)
H₂SO₄ + SO₃
<60°
o, p, and some m

(17)



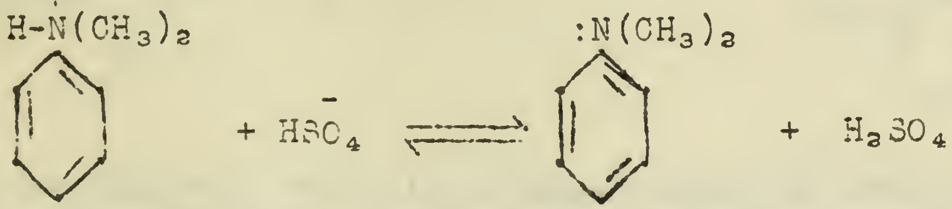
In the case of aniline freezing point and kinetic data indicate the intermediate formation of an aniline-SO_3 complex.

(18)



By virtue of the free electron pair on nitrogen the complex orients ortho-para at high or at low temperatures. Steric hindrance ("F-strain") prevents the formation of a complex such as [A] when dimethylaniline is used, and consequently sulfonation of the dimethylanilinium ion occurs in the meta position. It is interesting that the high temperature sulfonation of dimethylaniline cannot be carried out unless water is allowed to escape from the reaction mixture. This implies that sulfonation under these conditions must be preceded by the dissociation:

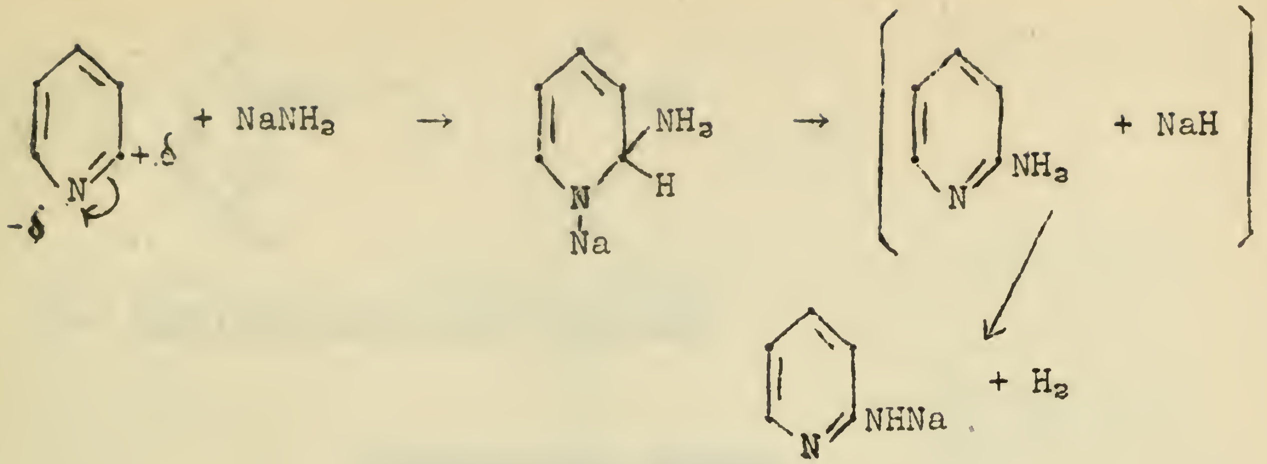
(19)



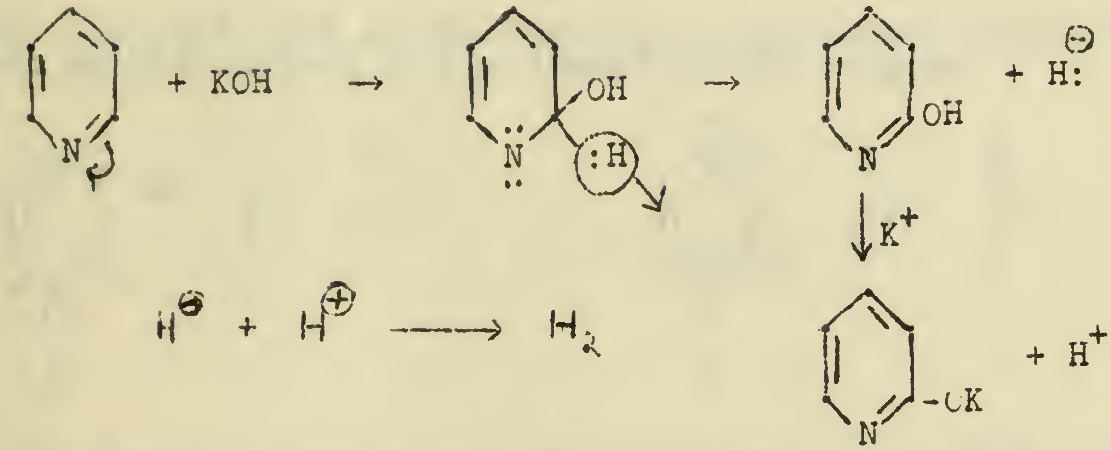
Free dimethylaniline is presumably the species which is sulfonated and it would be expected to orient ortho-para.

Nucleophilic Substitution

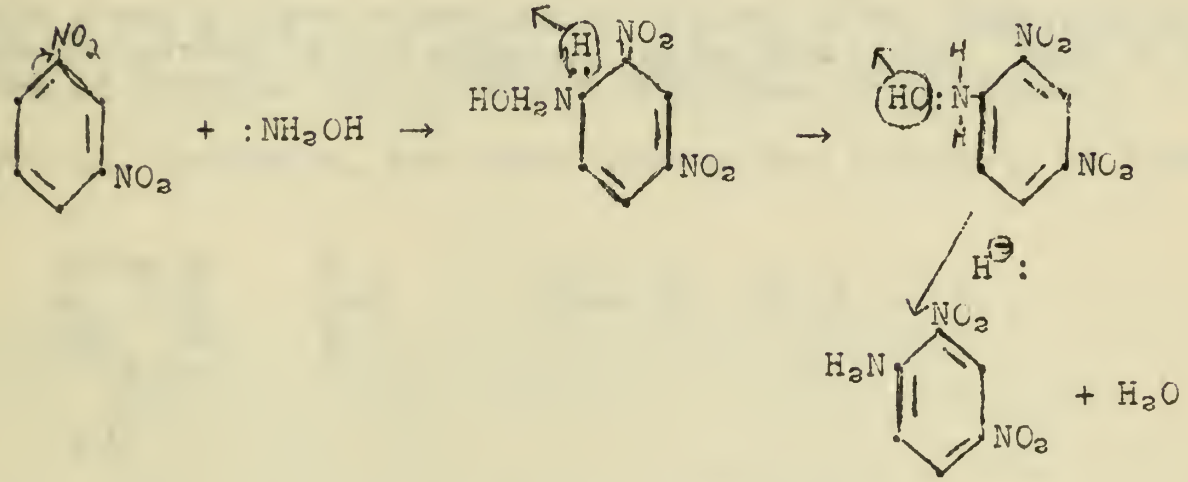
Reactions involving attack by nucleophilic reagents are known but are rather uncommon. Since the attack of the nucleophilic agent occurs at the carbon of lowest electron density, the rules of orientation are reversed. The following reactions appear to proceed by this mechanism:



(20)



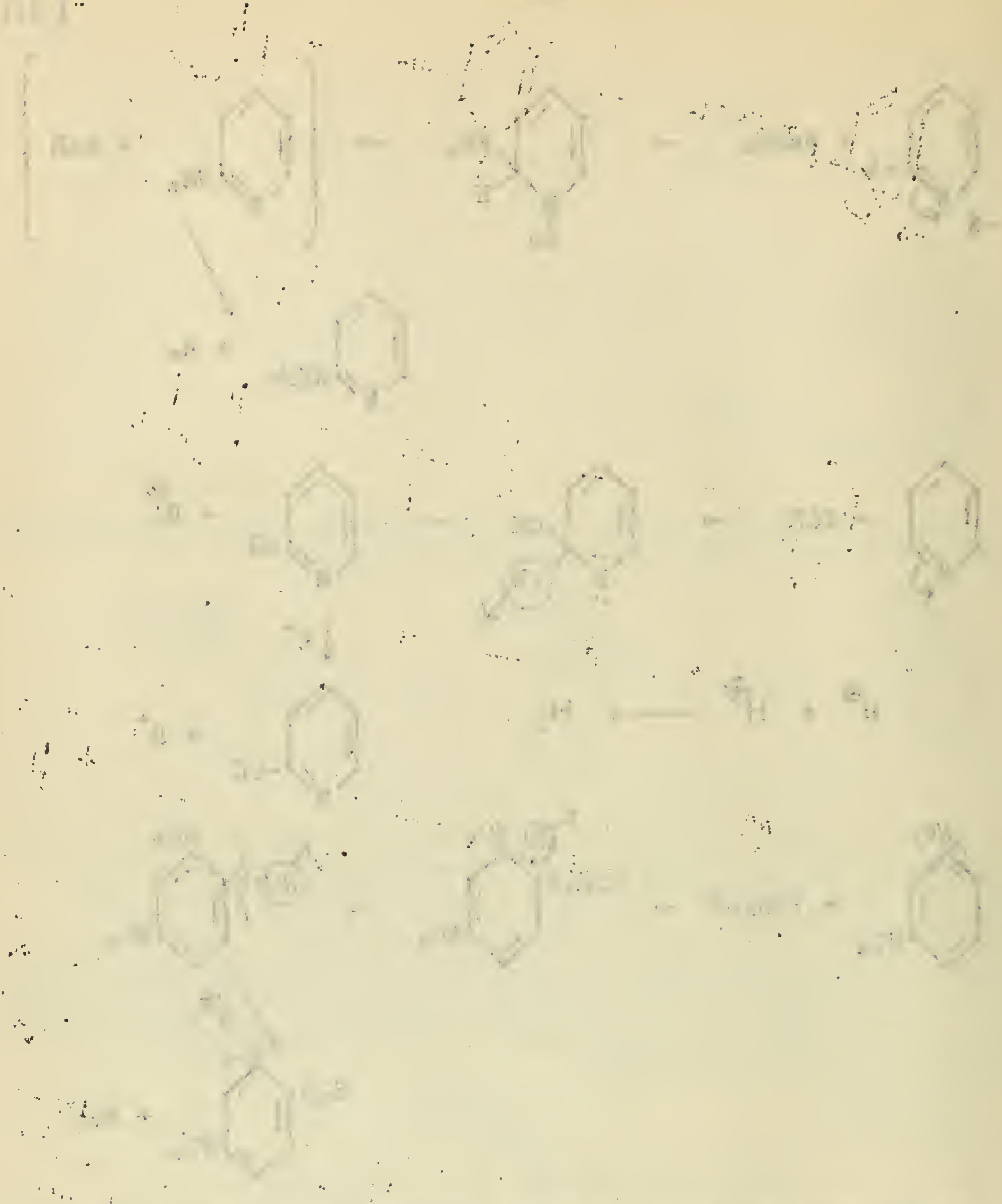
(21)



(22)

It will be observed that all of these examples involve the displacement of a hydride ion. The hydride ion may be transformed into molecular hydrogen by interaction with a proton from one of the reagents, or it may react to form water in the presence of oxygen.

Substituents other than hydrogen in activated positions may be displaced by nucleophilic reagents. The etherification of ortho or para negatively substituted halogen benzenes is an example of this type of reaction.



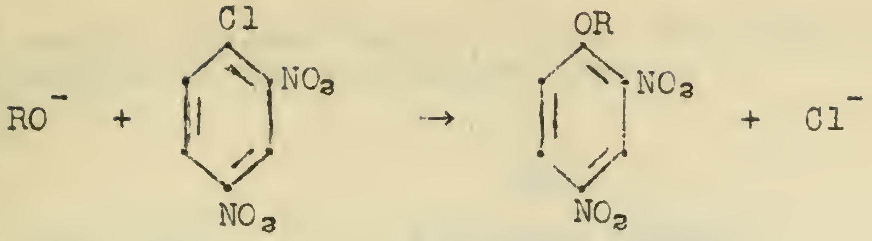
(20)

(21)

(22)

It will be observed that all of these examples involve the displacement of a hydroxyl group. The hydroxide ion may be transformed into molecular hydrogen by interaction with a proton (not one of the reactants), or it may react to form water in the presence of oxygen.

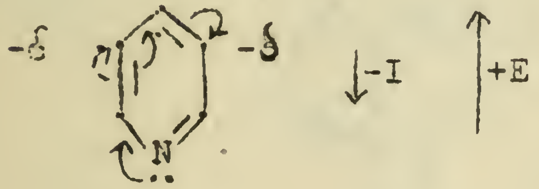
Substitution other than hydrogen in activated positions may be explained by nucleophilic reagents. The ammonolysis of ortho or para nuclearly substituted halogen compounds is an example of this type of reaction.

(23) 

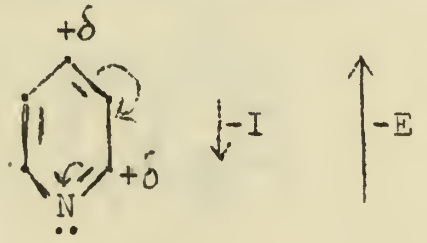
(See Etherification and Cleavage)

Heterocyclic Systems

The nitrogen atom in the pyridine nucleus may exhibit +E or -E electron shifts subject to the demand of the reagent.



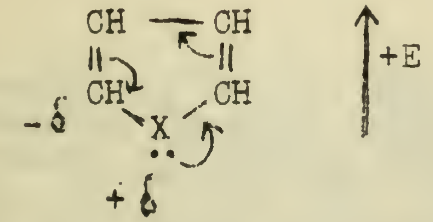
A



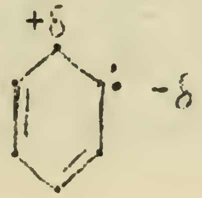
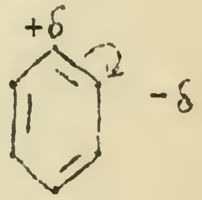
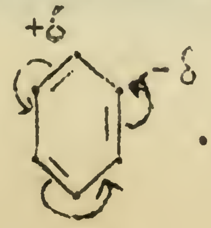
B

Both A and B favor electrophilic attack at the beta position and nucleophilic attack at the alpha and gamma positions. Many of the reactions of pyridine are in accord with these predictions.

Pyrrole, thiophene, and furan undergo the following +E electron shifts:



where X = NH, $\ddot{S}$, or $\ddot{O}$

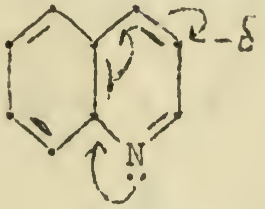
All are readily substituted in the alpha position by electrophilic reagents and are more susceptible to attack than benzene. It has been suggested that the reactivity in these structures may be attributed to a greater charge separation along the conjugate chain than in the corresponding transition states of benzene. It should be pointed out, however, that  may occur either by  or by .

A better explanation may lie in the amount of resonance lost in the formation of the transition states.

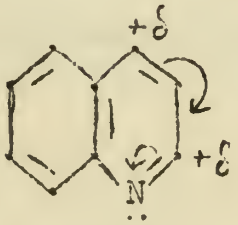
Table V

Substance	Resonance Energy (in K cal./mole)	Reactivity
Benzene	39	low
Thiophene	31	intermediate
Pyrrole	31	intermediate
Furan	23	great

Quinoline, like pyridine, may undergo electronic shifts subject to the demand of the reagent.



A



B

Quinoline may be monobrominated in the heterocyclic ring but is sulfonated and nitrated in the homocyclic ring. This would indicate that bromination involves structure A whereas sulfonation and nitration favor structure B, probably as a result of salt formation.

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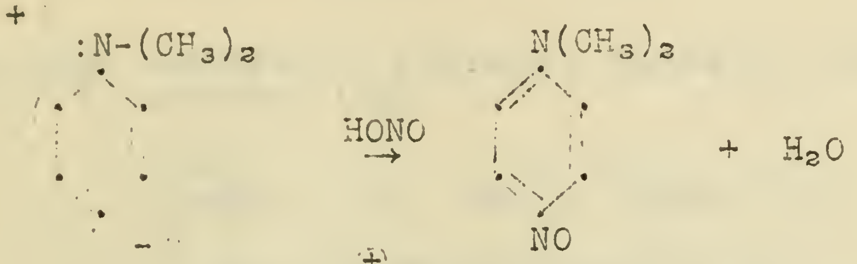
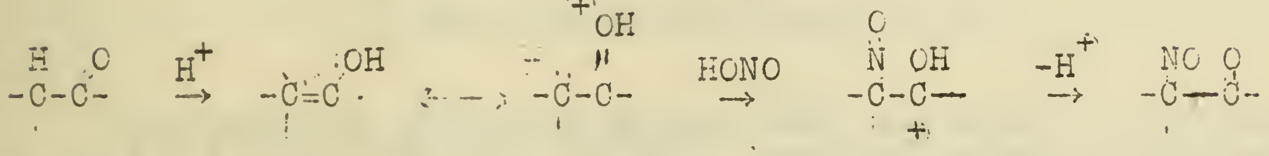
IONIC REACTIONS OF SOME COMPOUNDS CONTAINING NITROGEN TO NITROGEN BONDS

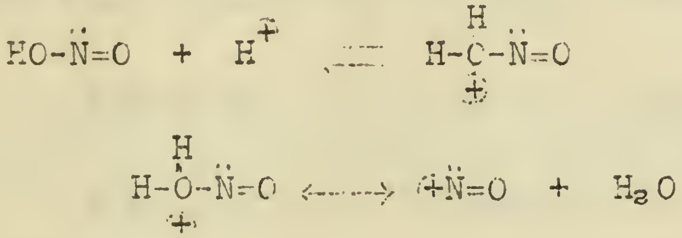
Diazotization.--It is well known that nitrous acid is an electrophilic reagent. In almost all of its reactions, it attacks a point of high electron density.





$$\overset{H}{-C}-\overset{O}{C}- \xrightarrow{H^+} -C=\overset{:OH}{C}- \dashrightarrow -\overset{\cdot\cdot}{C}-\overset{\overset{+}{O}H}{\overset{\|}{C}}- \xrightarrow{HONO} -\overset{\overset{O}{\vdots}}{\overset{N}{C}}-\underset{+}{\overset{OH}{C}}- \xrightarrow{-H^+} -\overset{NO}{C}-\overset{O}{C}-$$

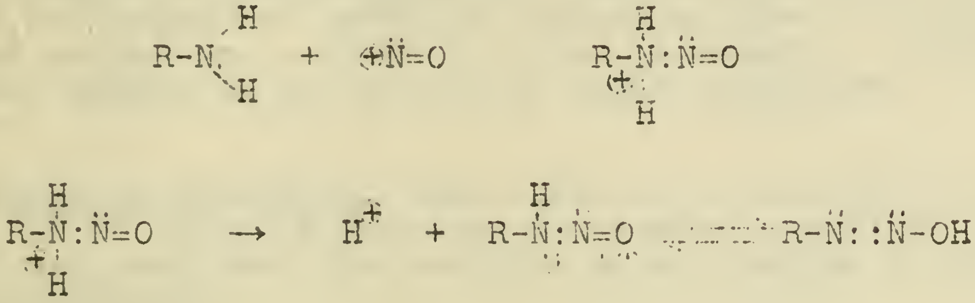
Presumably the function of a mineral acid is to facilitate the reaction:



$$HO-\ddot{N}=O + H^+ \rightleftharpoons H-\underset{+}{\overset{H}{C}}-\ddot{N}=O$$

$$H-\underset{+}{\overset{H}{O}}-\ddot{N}=O \longleftrightarrow {}^{+}\ddot{N}=O + H_2O$$

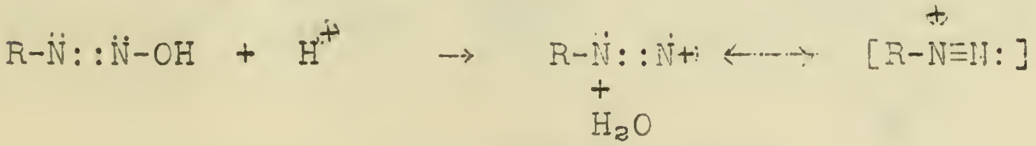
Accordingly, diazotization may be written:



$$R-N\begin{smallmatrix}H\\H\end{smallmatrix} + {}^{+}\ddot{N}=O \qquad R-\underset{\overset{+}{H}}{\overset{H}{\ddot{N}}}:\ddot{N}=O$$

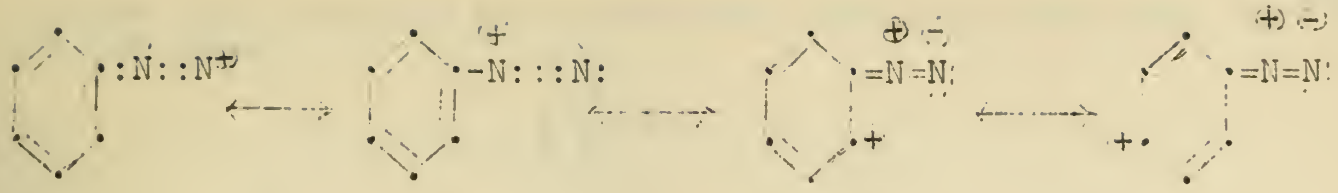
$$R-\underset{+\,H}{\overset{H}{\ddot{N}}}:\ddot{N}=O \rightarrow H^+ + R-\overset{H}{N}:\ddot{N}=O \rightleftharpoons R-\ddot{N}::\ddot{N}-OH$$

In the presence of excess acid, the diazonium hydroxide dissociates into a diazonium ion and water.



$$R-\ddot{N}::\ddot{N}-OH + H^+ \rightarrow \underset{\overset{+}{H_2O}}{R-\ddot{N}::N^{+}} \longleftrightarrow \overset{+}{[R-N\equiv N:]}$$

Undoubtedly, the same reaction occurs with primary amines and nitrous acid regardless of whether R is alkyl or aryl. In the case of aryl amines, the diazonium ion is stabilized by the resonance forms,



while the usual reaction of aliphatic amines is a decomposition into nitrogen and a carbonium ion.

$$R-\overset{+}{N}\equiv N: \quad \rightarrow \quad R^{+} \; + \; :N\equiv N:$$

(See "Carbonium Ions," p. 3)

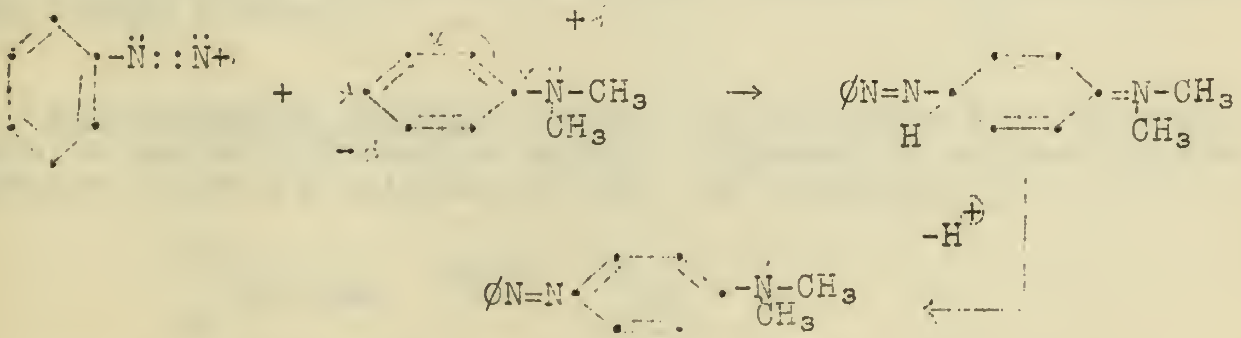
Reactions of Diazonium Salts.--The reactions of diazonium salts do not fit well into our scheme of reaction mechanisms probably because many of the reactions appear to proceed by free radical mechanisms. Thus, depending upon the environment of the diazonium salt, we may expect free radical (A) or ionic fission (B).

$$\phi:\ddot{N}::\ddot{N}:\ddot{Cl} \quad \rightarrow \quad \phi\cdot \; + \; \cdot\dot{N}::\dot{N}\cdot \; + \; \cdot\ddot{Cl}: \qquad (A)$$

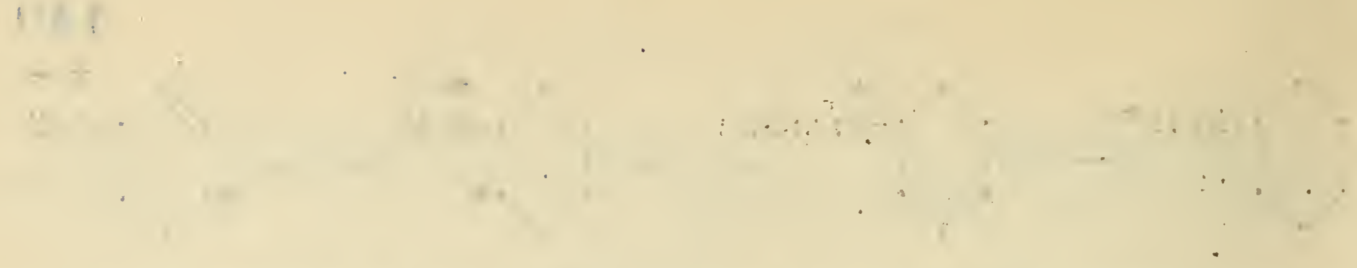
$$\phi:\ddot{N}::\ddot{N}:\ddot{Cl}: \quad \rightarrow \quad \phi:\ddot{N}::\ddot{N}^{+} \; + \; :\ddot{Cl}:^{-} \qquad (B)$$

The preparation of unsymmetrical biaryls, the Sandmeyer reaction, reductive deamonation, and the reaction of diazonium salts with α,β-unsaturated carbonyl compounds appear to proceed by free radical mechanisms, and will not be discussed. Coupling reactions, however, appear to proceed by an ionic mechanism.

Coupling Reactions.--The union of a diazonium component with a phenol or an amine is known as a diazonium coupling reaction. It is now believed that the reaction is an example of the usual aromatic substitution.



In terms of this mechanism, the fact that sodium acetate or sodium carbonate is usually necessary for coupling is readily understandable. In acid solution, there is little probability of collision



[illegible] decomposition into [illegible] carbonium ion.

$R{-}N_2^+ \rightarrow R^+ + N_2$

(see Kharasch [illegible], p. 5)

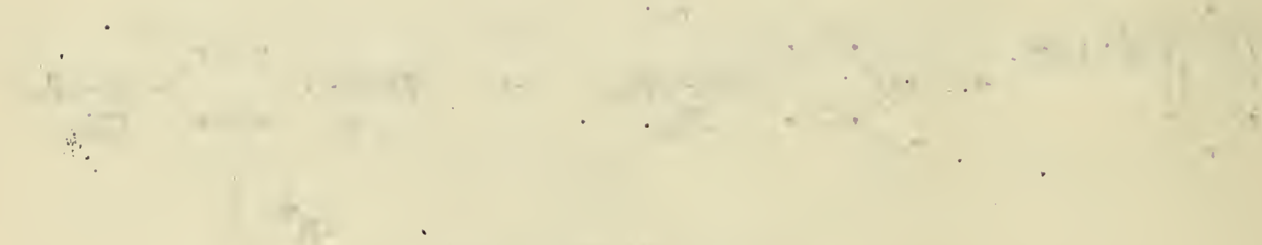
Reactions of Diazonium Salts.--[illegible]

[illegible] (a)

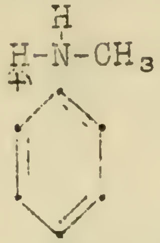
[illegible] (b)

The [illegible] however, [illegible]

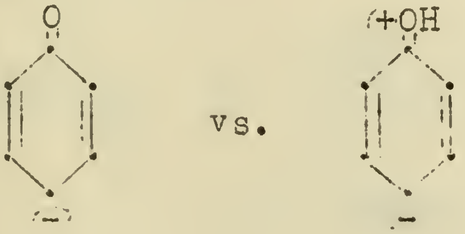
[illegible]--The [illegible]



In terms of this mechanism, the fact that [illegible] between the diazonium and substituted anilinium ion since they are of like sign.

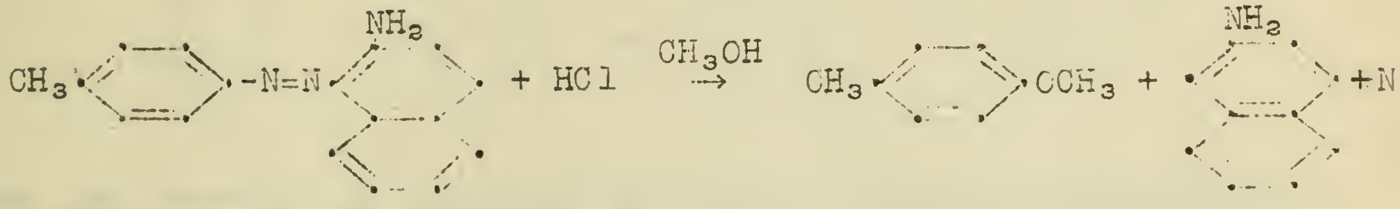


Further, the aromatic nucleus of the amine is deactivated. In the case of phenol, the phenolate ion not only has an opposite charge which is favorable for reaction, but also the electron density in the ortho and para position is much higher than in phenol itself, since



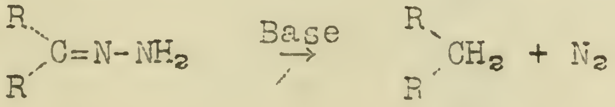
there is no restraining positive charge developed in the extreme resonance form. Electron-attracting groups such as p-nitro in the diazonium ion facilitates coupling by increasing the positive character and therefore the reactivity of the diazonium group.

It is interesting that the diazonium coupling reaction appears to be reversible in some cases. Thus, certain aryl-azo-β-naphthylamines are cleaved by alcoholic hydrochloric acid.



Undoubtedly, the reaction involves the displacement of the diazonium ion by a proton followed by the usual reaction of the diazonium ion with methyl alcohol.

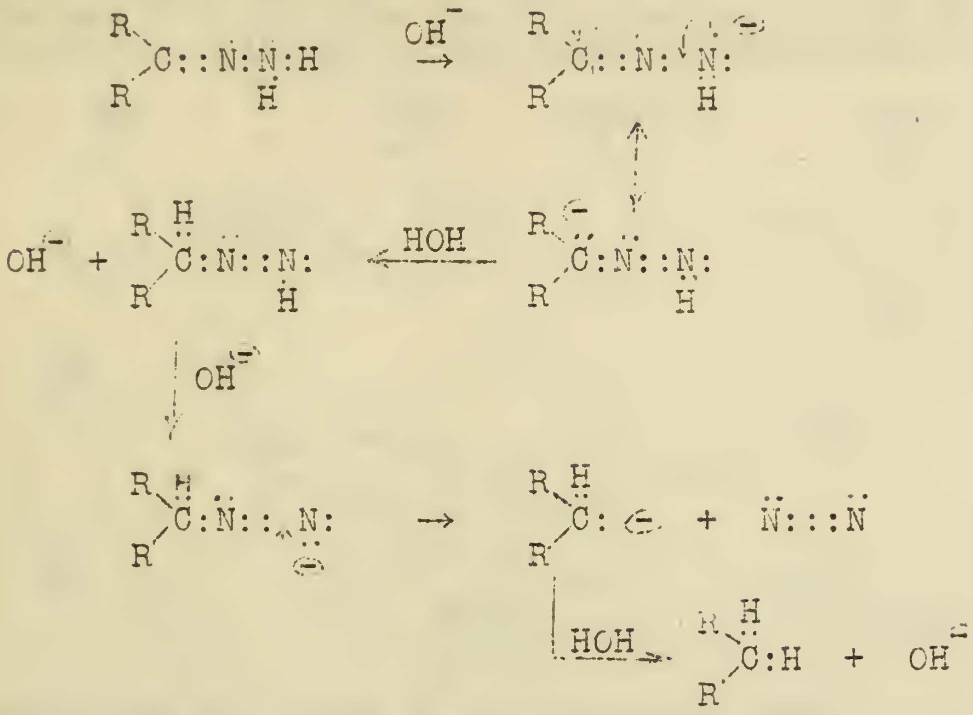
Wolff-Kishner Reaction.--When the hydrazone of a carbonyl compound is heated with strong alkali, nitrogen is evolved and two hydrogen atoms are introduced into the molecule.



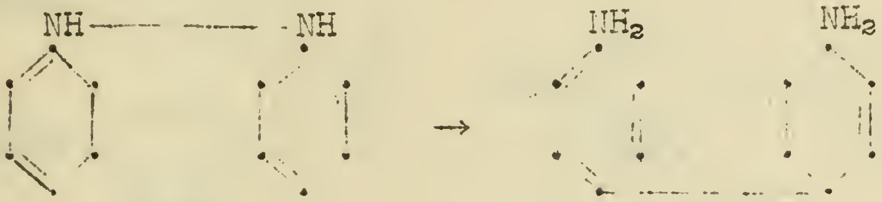
$$\begin{matrix}R\\ R'\end{matrix}\!\!>C=N-NH_2 \xrightarrow{\text{Base}} \begin{matrix}R\\ R'\end{matrix}\!\!>CH_2 + N_2$$

In early procedures anhydrous sodium ethylate was employed, but recently a technique has been developed using sodium hydroxide in diethylene glycol solution.

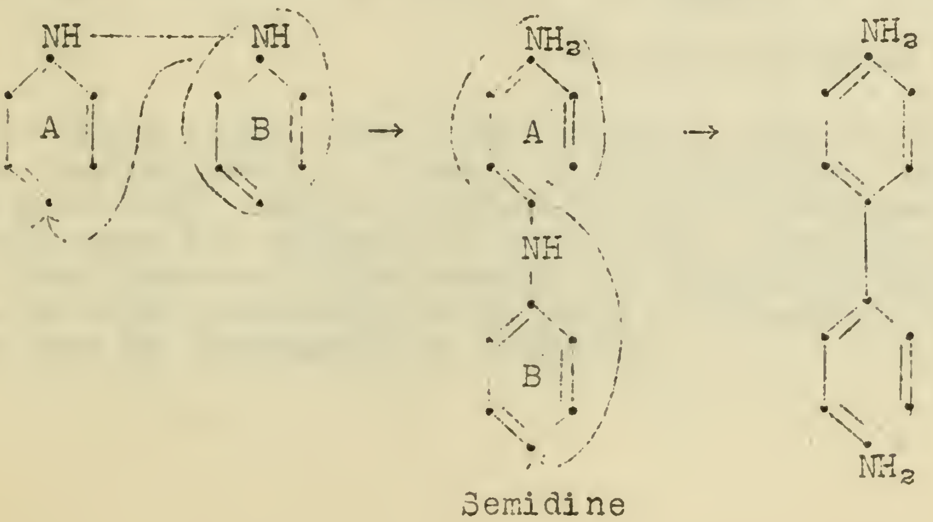
Little is known concerning the mechanism of this reaction. One possibility is shown below.


OH⁻
HOH
OH⁻
HOH

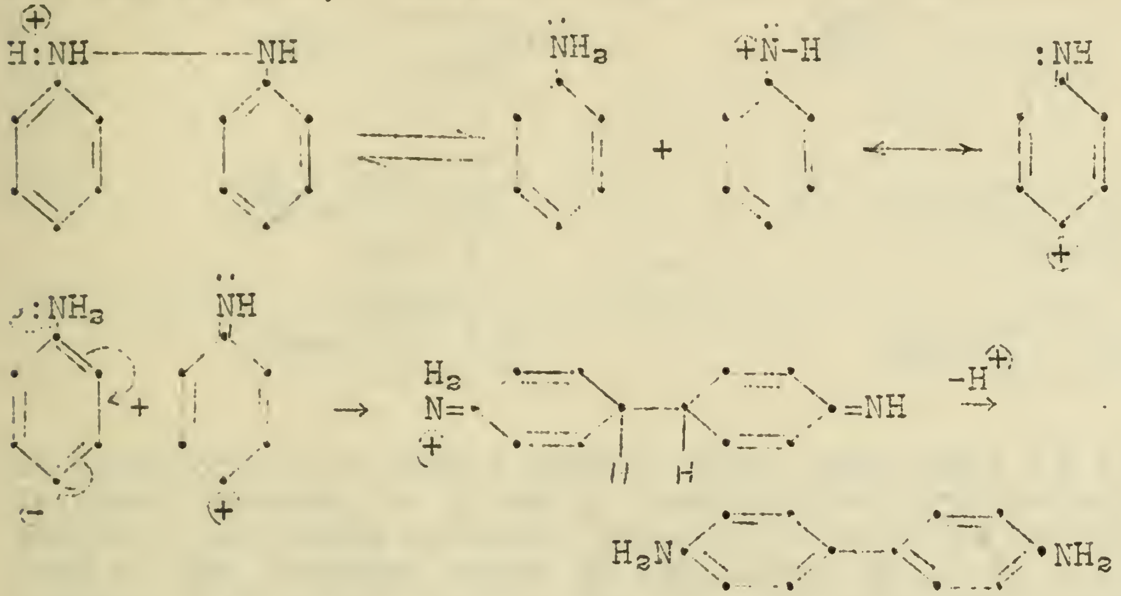
Benzidine Rearrangement.--The benzidine rearrangement in which hydrazobenzenes are transformed into derivatives of 4,4'-diaminodiphenyl (benzidine) has been the subject of considerable theoretical speculation.


NH
NH
NH₂
NH₂

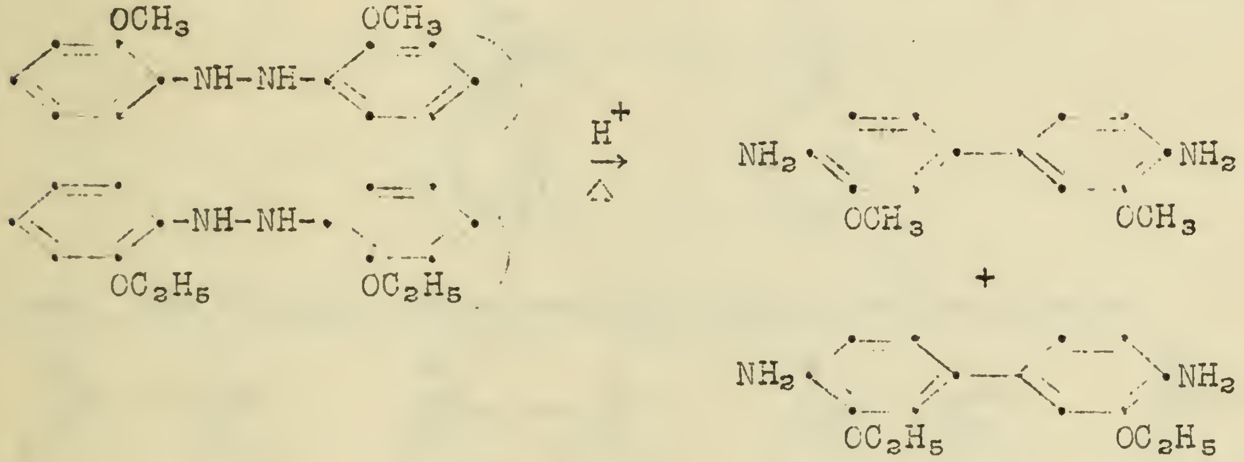
Since the reaction is catalyzed by acid and bears a formal resemblance to the Fischer-Hepp rearrangement and related reactions, it was originally supposed that the reaction proceeded as follows:


NH
NH
A
B
NH₂
A
NH
B
Semidine
NH₂
NH₂

Experiment has shown, however, that semidine is not converted into benzidine in the presence of acid. Another attractive mechanism for the transformation involves the dissociation of the N-N link into an ion and aniline, followed by the usual electrophilic attack.

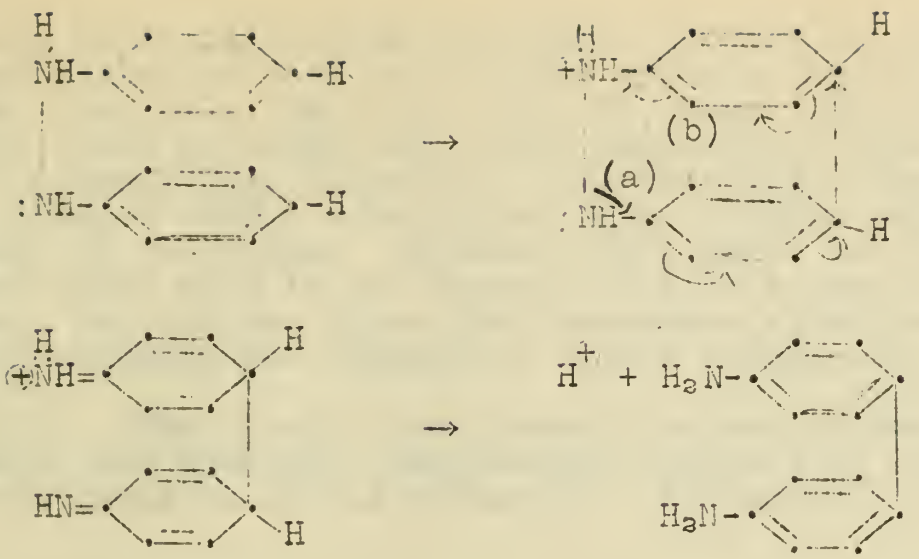

H:NH
NH
NH₃
N-H
:NH
:NH₃
NH
H₂
N=
=NH
-H
H
H
H₂N
NH₂

This possibility too seems to be ruled out since no mixed benzidines are obtained when equimolar proportions of o,o'-dimethoxy-hydrazobenzene and o,o'-diethoxy-hydrazobenzene are rearranged together.


OCH₃
OCH₃
-NH-NH-
-NH-NH-
OC₂H₅
OC₂H₅
H⁺
NH₂
NH₂
OCH₃
OCH₃
+
NH₂
NH₂
OC₂H₅
OC₂H₅

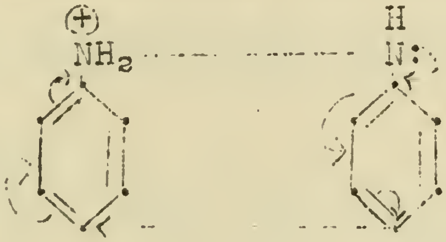
(No mixed product formed)

In view of these facts, the transformation seems to be an intramolecular rearrangement. Towards this conclusion, Ingold and Robinson have both proposed intramolecular mechanisms which appear to be based upon the assumption that in the transition state, the p and p' positions are close enough for incipient bond formation. While it is only a description of what is thought to happen, the situation may be diagrammed as follows:

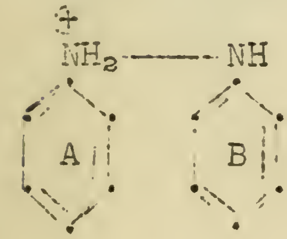


An examination of Stuart models shows that there is considerable distance between the p and p' positions of hydrazobenzene even in the most favorable position possible regardless of whether one or both of the nitrogen atoms is considered to be in a quaternary form. Another difficulty lies in the proposed electron recession from a positively charged center (a). In addition, shift (b) would postulate a five covalent nitrogen atom.

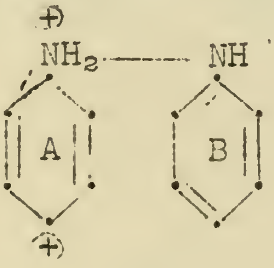
If the electromeric effects are postulated as follows:



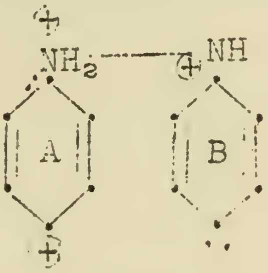
Then, the various structures that might be formed are:



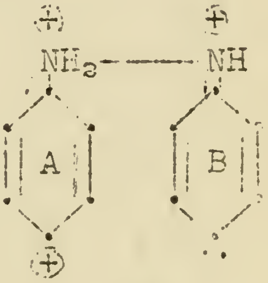
I



II



III



IV

The distance between the p-carbon atoms in (I) is found to be 4.26Å. In (II), the minimum distance would be 1.50Å, since the charged nitrogen atom is no longer in the plane of the attached benzene ring. Para bonding would be possible in this structure - the single carbon-to-carbon bond distance being 1.54Å. This structure by itself cannot

represent the activated transition state, because it indicates none of the polarization effects in (B) that would be set up by the highly polar ring (A). In (III) and (IV), where the minimum *p*-separation would be 1.68Å and 2.71Å respectively, the ring (B) *p*-positions possess this polarity. Structure (III) possesses a positively charged carbon atom linked to a nitrogen atom with an unshared pair of electrons. Structure (IV) might be expected to play a significant role in the transition hybrid were it not for the fact that Pauling has shown that resonance structures having adjacent like charged are usually of little importance.

In short: "The change thus seems to be an intramolecular rearrangement, but there is insufficient evidence to support any definite hypothesis as to its mechanism" (Sidgwick, p. 387).

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